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(54) Title: INHIBITORS OF PHOSPHOLIPASE ENZYMES

(57) Abstract

Novel compounds are disclosed which inhibit the activity of phospholipase enzymes, particularly cytosolic phospholipase A_2. Pharmaceutical compositions comprising such compounds and methods of treatment using such compositions are also disclosed.

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INHIBITORS OF PHOSPHOLIPASE ENZYMES

Background of the Invention

The present invention relates to chemical inhibitors of the activity of various phospholipase enzymes, particularly phospholipase A_2 enzymes.

Leukotrienes and prostaglandins are important mediators of inflammation, each of which classes contributes to the development of an inflammatory response in a different way. Leukotrienes recruit inflammatory cells such as neutrophils to an inflamed site, promote the extravasation of these cells and stimulate release of superoxide and proteases which damage the tissue. Leukotrienes also play a pathophysiological role in the hypersensitivity experienced by asthmatics [See, e.g. B. Samuelson et al., Science, 237:1171-76 (1987)]. Prostaglandins enhance inflammation by increasing blood flow and therefore infiltration of leukocytes to inflamed sites. Prostaglandins also potentiate the pain response induced by stimuli.

Prostaglandins and leukotrienes are unstable and are not stored in cells, but are instead synthesized [W. L. Smith, Biochem. J., 259:315-324 (1989)] from arachidonic acid in response to stimuli. Prostaglandins are produced from arachidonic acid by the action of COX-1 and COX- 2 enzymes. Arachidonic acid is also the substrate for the distinct enzyme pathway leading to the production of leukotrienes.

Arachidonic acid which is fed into these two distinct inflammatory pathways is released from the sn-2 position of membrane phospholipids by phospholipase A_2 enzymes (hereinafter PLA_2). The reaction catalyzed by PLA_2 is believed to represent the rate-limiting step in the process of lipid mediated biosynthesis and the production of inflammatory prostaglandins and leukotrienes. When the phospholipid substrate of PLA_2 is of the phosphotidyl choline class with an ether linkage in the sn-1 position, the lysophospholipid produced is the immediate precursor of platelet activating factor (hereafter called PAF), another potent mediator of inflammation [S.I. Wasserman, Hospital Practice, 15:49-58 (1988)].

Most anti-inflammatory therapies have focussed on preventing production of either prostglandins or leukotrienes from these distinct pathways, but not on all of them. For example, ibuprofen, aspirin, and indomethacin are all NSAIDs which inhibit the production of prostaglandins by COX-1/COX-2, but have no effect on the inflammatory production of leukotrienes from arachidonic acid in the other pathways. Conversely, zileuton inhibits only the pathway of conversion of arachidonic acid to leukotriense, without affecting the production of prostaglandins. None of these widely-used anti-inflammatory agents affects the production of PAF.

Consequently the direct inhibition of the activity of PLA_2 has been suggested as a useful mechanism for a therapeutic agent, i.e., to interfere with the inflammatory response. [See, e.g., J. Chang et al, Biochem. Pharmacol., 36:2429-2436 (1987)].

A family of PLA_2 enzymes characterized by the presence of a secretion signal sequenced and ultimately secreted from the cell have been sequenced and structurally defined. These secreted PLA_2s have an approximately 14 kD molecular weight and contain seven disulfide bonds which are necessary for activity. These PLA_2s are found in large quantities in mammalian pancreas, bee venom, and various snake venom. [See, e.g., references 13-15 in Chang et al, cited above; and E. A. Dennis, Drug Devel. Res., 10:205-220 (1987).] However, the pancreatic enzyme is believed to serve a digestive function and, as such, should not be important in the production of the inflammatory mediators whose production must be tightly regulated.

The primary structure of the first human non-pancreatic PLA_2 has been determined. This non-pancreatic PLA_2 is found in platelets, synovial fluid, and spleen and is also a secreted enzyme. This enzyme is a member of the aforementioned family. [See, J. J. Seilhamer et al, J. Biol. Chem., 264:5335-5338 (1989); R. M. Kramer et al, J. Biol. Chem., 264:5768-5775 (1989); and A. Kando et al, Biochem. Biophys. Res. Comm., 163:42-48 (1989)]. However, it is doubtful that this enzyme is important in the synthesis of prostaglandins, leukotrienes and PAF, since the non-pancreatic PLA_2 is an extracellular protein which would be difficult to regulate, and the next enzymes in the biosynthetic pathways for these compounds are intracellular proteins. Moreover, there is evidence that PLA_2 is regulated by protein kinase C and G proteins [R. Burch and J. Axelrod, Proc. Natl. Acad. Sci. U.S.A., 84:6374-6378 (1989)] which are cytosolic proteins which must act on intracellular proteins. It would be impossible for the non-pancreatic PLA_2 to function in the cytosol, since the high reduction potential would reduce the disulfide bonds and inactivate the enzyme.

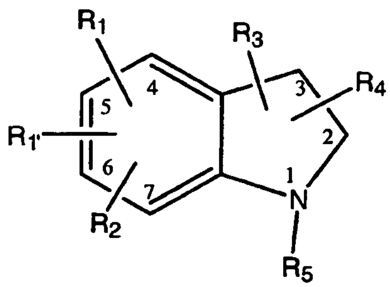
A murine PLA_2 has been identified in the murine macrophage cell line, designated RAW 264.7. A specific activity of 2 mols/min/mg, resistant to reducing conditions, was reported to be associated with the approximately 60 kD molecule. However, this protein was not purified to homogeneity. [See, C. C. Leslie et al, Biochem. Biophys. Acta., 963:476-492 (1988)]. The references cited above are incorporated by reference herein for information pertaining to the function of the phospholipase enzymes, particularly PLA_2.

A cytosolic phospholipase A_2 (hereinafter "$cPLA_2$") has also been identified and cloned. See, U.S. Patent Nos. 5,322,776 and 5,354,677, which are incorporated herein by reference as if fully set forth. The enzyme of these patents is an intracellular PLA_2 enzyme, purified from its natural source or otherwise produced in purified form, which functions intracellularly to produce arachidonic acid in response to inflammatory stimuli.

Now that several phospholipase enzymes have been identified, it would be desirable to identify chemical inhibitors of the action of enzymes, which inhibitors could be used to treat inflammatory conditions, particularly where inhibition of production of prostaglandins, leukotrienes and PAF are all desired results. There remains a need in the art for an identification of such anti-inflammatory agents for therapeutic use in a variety of disease states.

<u>Summary of the Invention</u>

Compounds of this invention have the following formulae:



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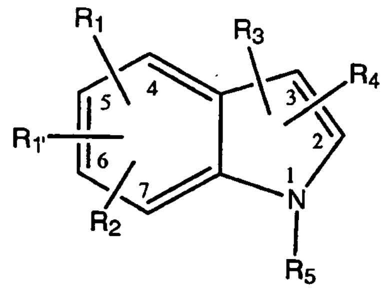
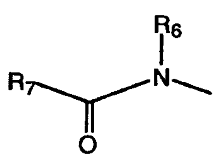
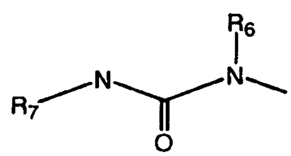
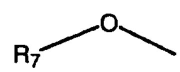


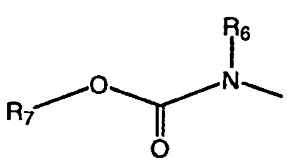
wherein:

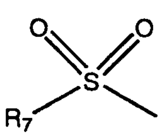
R_1 and $R_{1'}$ are independently selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_{10} alkyl, preferably $-C_1$-C_6 alkyl, $-S$-C_1-C_{10} alkyl, preferably $-S$-C_1-C_6 alkyl, C_1-C_{10} alkoxy, preferably C_1-C_6 alkoxy, -CN, $-NO_2$, $-NH_2$, $-HN(C_1$-$C_6)$, $-N(C_1$-$C_6)_2$, phenyl, -O-phenyl, -S-phenyl, benzyl, -O-benzyl, -S-benzyl or a moiety of the formulae:

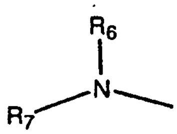
,

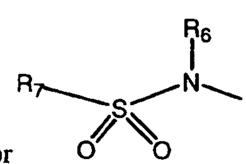
,

,

,

,

, or

;

R_6 is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, -O-phenyl, benzyl, -O-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, -CN, -CF_3, or -OH;

R_7 is selected from -OH, $-CF_3$, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NH-(C_1-C_6 alkyl), -N-(C_1-C_6 alkyl)$_2$, pyridinyl, thienyl, furyl, pyrrolyl, phenyl, -O-phenyl, benzyl, -O-benzyl, the rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, $-CF_3$, or -OH;

R_2 is selected from H, halogen, $-CF_3$, -OH, -C_1-C_{10} alkyl, preferably -C_1-C_6 alkyl, C_1-C_{10} alkoxy, preferably C_1-C_6 alkoxy, -CHO, -CN, $-NO_2$, $-NH_2$, -NH-C_1-C_6 alkyl, -N(C_1-C_6 alkyl)$_2$, -N-SO_2-C_1-C_6 alkyl, or -SO_2-C_1-C_6 alkyl;

R_3 is selected from H, $-CF_3$, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, C_3-C_{10} cycloalkyl, -C_1-C_6 alkyl-C_3-C_{10} cycloalkyl, -CHO, halogen, or a moiety of the formula -L^2-M^2:

L^2 indicates a linking or bridging group of the formulae -$(CH_2)_n$-, -S-, -O-, -C(O)-, -$(CH_2)_n$-C(O)-, -$(CH_2)_n$-C(O)-$(CH_2)_n$-, -$(CH_2)_n$-O-$(CH_2)_n$-, or -$(CH_2)_n$-S-$(CH_2)_n$-, -C(O)C(O)X;
where X = O,N

M^2 is selected from the group of C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, C_3-C_{10} cycloalkyl, phenyl or benzyl, the cycloalkyl, phenyl or benzyl rings being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_{10} alkyl, preferably C_1-C_6 alkyl, C_1-C_{10} alkoxy, preferably C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, -CN, or $-CF_3$; or

a) a five-membered heterocyclic ring containing one or two ring heteroatoms selected from N, S or O including, but not limited to, furan, pyrrole, thiophene, imidazole, pyrazole, pyrrolidine, or tetrazole, the five-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_{10} alkyl, preferably C_1-C_6 alkyl, C_1-C_{10} alkoxy, preferably C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, -CN, or -CF_3; or

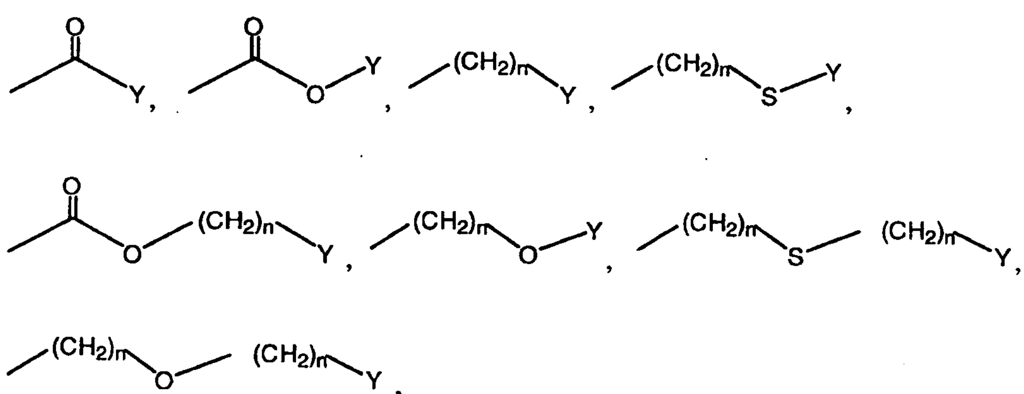
b) a six-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, S or O including, but not limited to pyridine, pyrimidine, piperidine, piperazine, or morpholine, the six-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_{10} alkyl, preferably C_1-C_6 alkyl, C_1-C_{10} alkoxy, preferably C_1-C_6 alkoxy, -CHO, -NO_2, -NH_2, -CN, -CF_3 or -OH; or

c) a bicyclic ring moiety containing from 8 to 10 ring atoms and optionally containing from 1 to 3 ring heteroatoms selected from N, S or O including, but not limited to benzofuran, indole, indoline, napthalene, purine, or quinoline, the bicyclic ring moiety being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_{10} alkyl, preferably C_1-C_6 alkyl, C_1-C_{10} alkoxy, preferably C_1-C_6 alkoxy, -CHO, -NO_2, -NH_2, -CN, -CF_3 or -OH;

n is an integer from 0 to 3;

R_4 is selected from the group of C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, -$(CH_2)_n$-C_3-C_6 cycloalkyl, -$(CH_2)_n$-S-$(CH_2)_n$-C_3-C_5 cycloalkyl, -$(CH_2)_n$-O-$(CH_2)_n$-C_3-C_5 cycloalkyl, or the groups of:

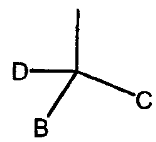
a) -$(CH_2)_n$-phenyl-O-phenyl, -$(CH_2)_n$-phenyl-CH_2-phenyl, -$(CH_2)_n$-O-phenyl-CH_2-phenyl, -$(CH_2)_n$-phenyl-(O-CH_2-phenyl)$_2$, -CH_2-phenyl-C(O)-benzothiazole or a moiety of the formulae:



wherein n is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2, Y is C_3-C_5 cycloalkyl, phenyl, benzyl, napthyl, pyridinyl, quinolyl, furyl, thienyl or pyrrolyl; rings of these groups being optionally substituted by from 1 to 3 substituents selected from H, halogen, -CF_3, -OH, -C_1-C_6 alkyl, C_1-C_6 alkoxy, -NH_2, -NO_2 or a five membered

heterocyclic ring containing one heteroatom selected from N, S, or O, preferably S or O; or

b) a moiety of the formulae $-(CH_2)_n$-A, $-(CH_2)_n$-S-A, or $-(CH_2)_n$-O-A, wherein A is the moiety:

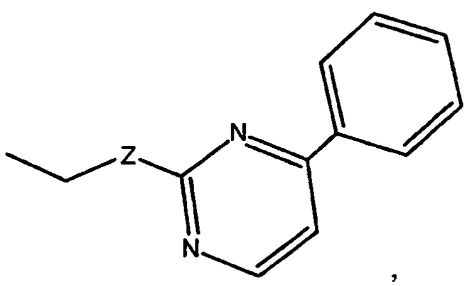


wherein

D is H, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, or $-CF_3$;

B and C are independently selected from phenyl, pyridinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, preferably 1 to 2, substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, or $-NO_2$; or

c) a moiety of the formulae:



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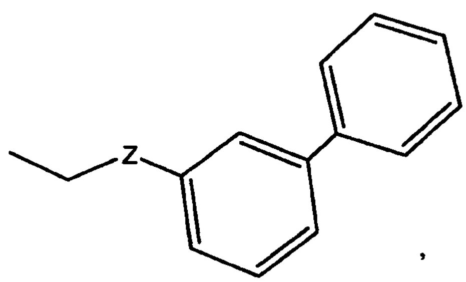

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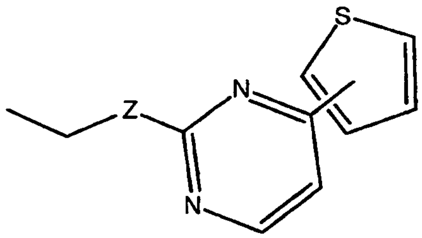
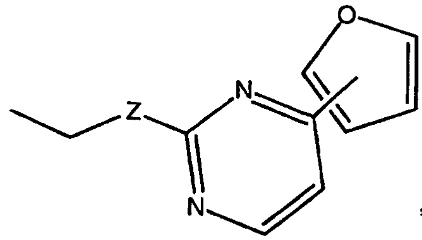
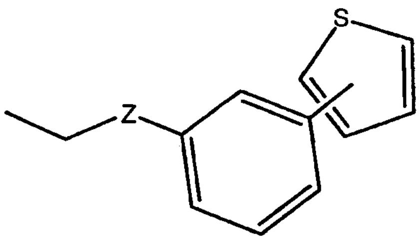
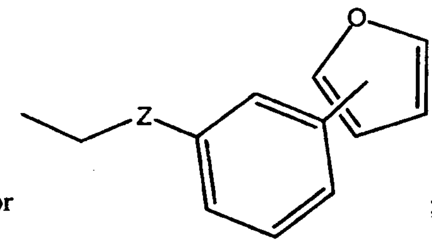
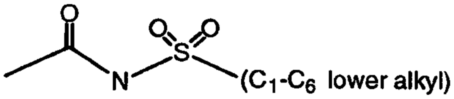
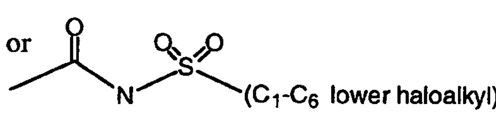
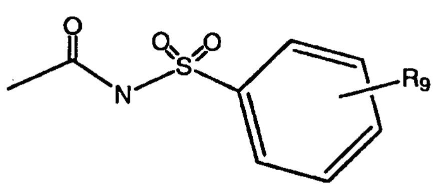
 ,  ,

 , or  ;

wherein Z is O or S and the phenyl and pyrimidinyl rings of each moiety are optionally and independently substituted by from 1 to 3 substituents selected from halogen, $-CF_3$, -OH, $-C_1-C_6$ alkyl, C_1-C_6 alkoxy, $-NH_2$, or $-NO_2$;

R_5 is selected from -COOH, -C(O)-COOH, $-(CH_2)_n$-C(O)-COOH, $-(CH_2)_n$-COOH, -CH=CH-COOH, $-(CH_2)_n$-tetrazole,

or  or  or

 or

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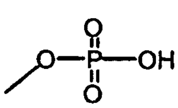
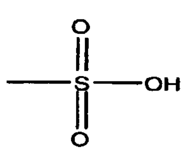
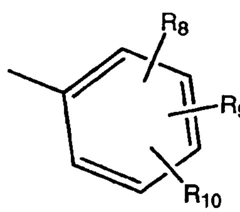
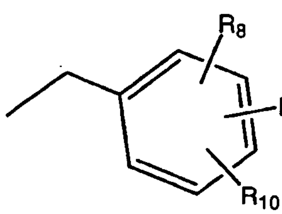
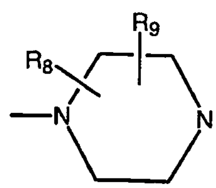
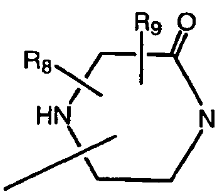
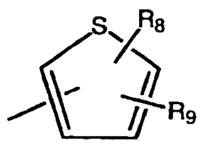
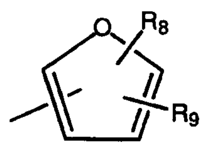
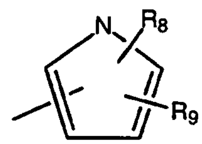
 or 

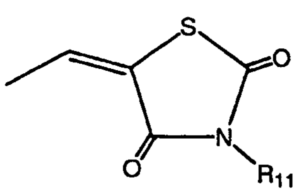
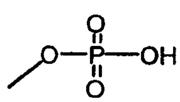
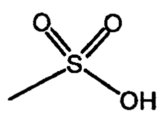
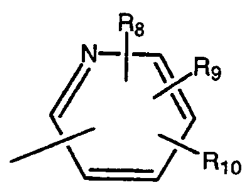
or a moiety selected from the formulae -L[1]-M[1];

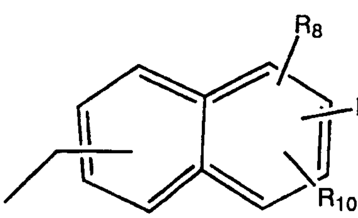
wherein L[1] is a bridging or linking moiety selected from a chemical bond, $-(CH_2)_n-$, -S-, -O-, -C(O)-, $-(CH_2)_n-C(O)-$, $-(CH_2)_n-C(O)-(CH_2)_n-$, $-(CH_2)_n-O-(CH_2)_n-$,$-(CH_2)_n-S-(CH_2)_n-$, $-C(Z)-N(R_6)-$, $-C(Z)-N(R_6)-(CH_2)_n-$, $-C(O)-C(Z)-N(R_6)-$, $-C(O)-C(Z)-N(R_6)-(CH_2)_n-$, $-C(Z)-NH-SO_2-$, or $-C(Z)-NH-SO_2-(CH_2)_n-$;

M[1] is selected from the group of -COOH, $-(CH_2)_n-COOH$, $-(CH_2)_n-C(O)-COOH$, tetrazole,

 ,  ,  ,

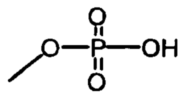
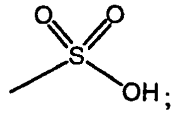
 ,  ,  ,  ,

 ,  ,  or 



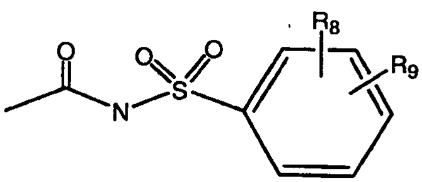
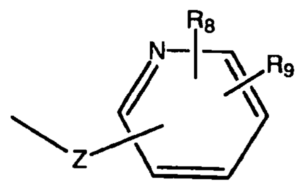
where R_8, R_9 or R_{10} can be attatched anywhere in the cyclic or bicyclic system,

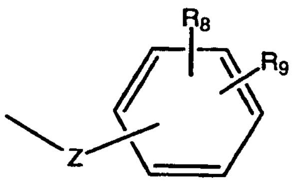
R_8, in each appearance, is independently selected from H, -COOH, $-(CH_2)_n-COOH$, $-(CH_2)_n-C(O)-COOH$, tetrazole,

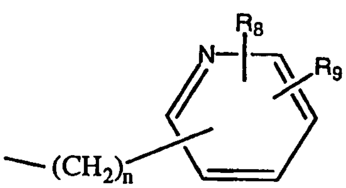
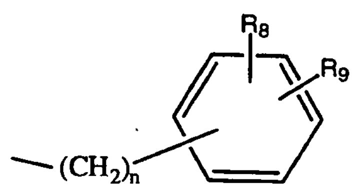
, or ;

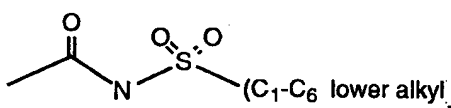
R_9 is selected from H, halogen, $-CF_3$, -OH, -COOH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH, $-C_1$-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), or -N(C_1-C_6 alkyl$)_2$;

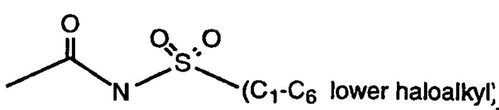
R_{10} is selected from the group of H, halogen, $-CF_3$, -OH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH, $-C_1$-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl$)_2$,

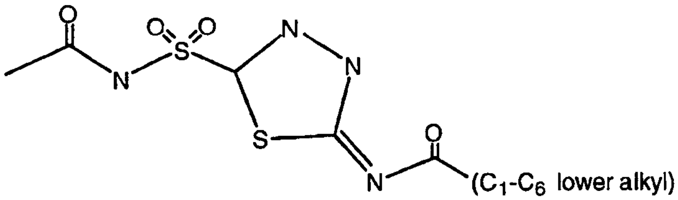
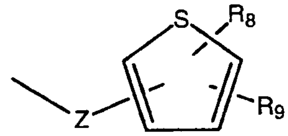
, ,

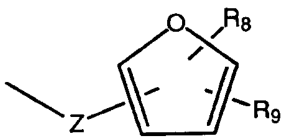
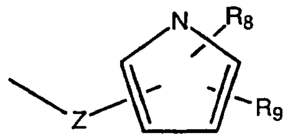
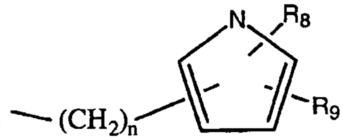
,

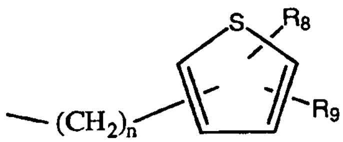
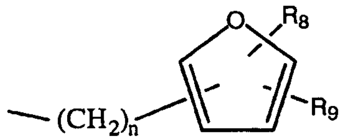
, ,

or ,

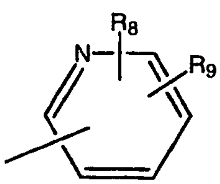
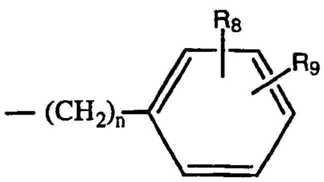
or ,

,
,

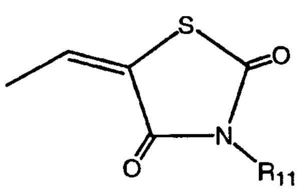
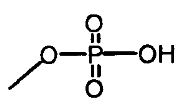
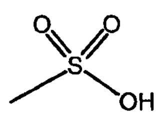
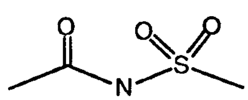
,

,

, or
;

R_{11} is selected from H, C_1-C_6 lower alkyl, C_1-C_6 cycloalkyl, $-CF_3$, -COOH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH,

,
;

with a proviso that the complete moiety at the indole or indoline 1-position created by any combination of R_5, R_8, R_9, R_{10}, and/or R_{11} shall contain at least one acidic moiety selected from or containing a carboxylic acid, a tetrazole, or a moiety of the formulae:

,
,
 or
;

n is an integer from 0 to 3;
or a pharmaceutically acceptable salt thereof.

It will be understood in the group above that substituents R_3 and R_4 are bound to the indole or indoline ring's 2- or 3-position and the R_1, $R_{1'}$ and R_2 groups are bound to one of the indole or indoline ring's 4-, 5-, 6- or 7-position carbon atoms.

One group of compounds within this invention are those in which the $R_{1'}$ and R_3 groups are hydrogen and the substituents at the other indole or indoline positions are as described above.

Another group of this invention comprises compounds in which the $R_{1'}$ and R_3 groups are hydrogen and the groups at R_1, R_4, and R_5 are as defined above. Within this group are two further preferred groups. In the first, R_1 is in the indole or indoline 5-position and in the second R_1 is in the indole or indoline 6 position.

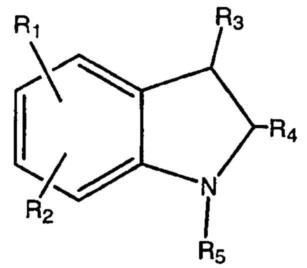
In a further preferred group herein, R_1 is in the indole or indoline 5-position and is benzyloxy, R_2 and R_4 are hydrogen and R_3 and R_5 are as defined above.

In an another preferred group of this invention R_1 is in the indole or indoline 5 or 6 position and is cyclopentylcarboxamide or cyclopentyloxycarbonylamino, R_2 and R_4 are hydrogen, and R_3 and R_5 are as defined above.

A further preferred group of this invention consists of R_1 and R_2at the indole or indoline 5 and or 6 position and are each selected from the group consisting of C_1-C_6alkoxy, cyano, sulfonyl and halo, R_2 and R_4 are hydrogen, and R_3 and R_5 are as defined above.

It is also understood that there is a further preferred subgroup within each of the groups set forth herein wherein the core molecule is an indole moiety, rather than an indoline. There is also understood to be a second group within each wherein the core molecule is an indoline moiety.

Preferred compounds of this invention include those of the following formulae:



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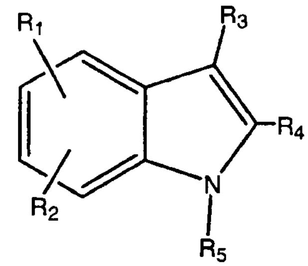
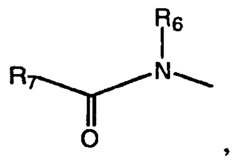
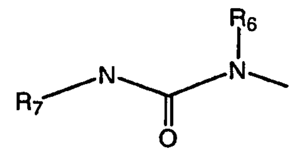
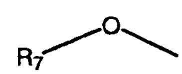


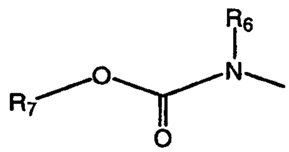
wherein:

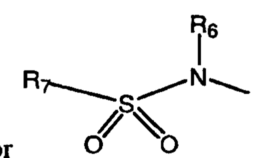
R_1 is selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, $-HN(C_1$-$C_6)$, $-N(C_1$-$C_6)_2$, phenyl, -O-phenyl, benzyl, -O-benzyl, or a moiety of the formulae:

 ,

 ,

 ,

 ,

or  ;

R_6 is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, -O-phenyl, benzyl, -O-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NH_2$, $-NO_2$, $-CF_3$, or -OH;

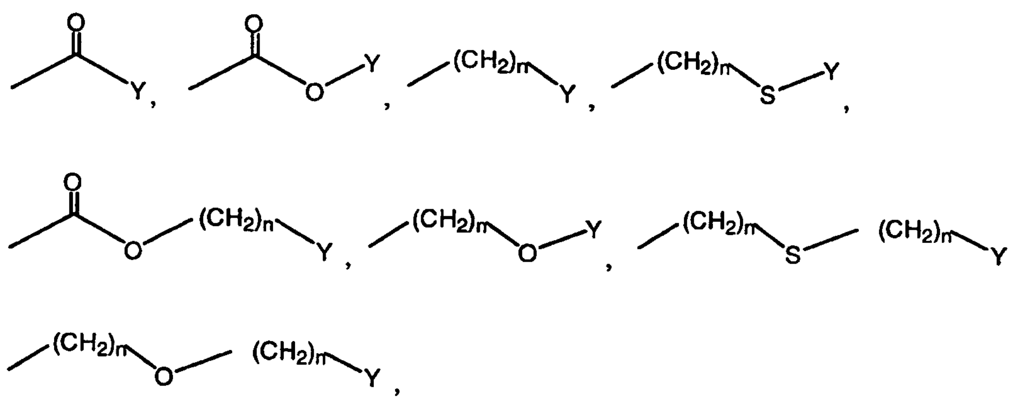
R_7 is selected from $-(CH_2)_n$-COOH, $-(CH_2)_n$-N-$(C_1$-C_6 alkyl$)_2$, $-(CH_2)_n$-NH-$(C_1$-C_6 alkyl), $-CF_3$, C_1-C_6 alkyl, C_3-C_5 cycloalkyl, C_1-C_6 alkoxy, -NH-$(C_1$-C_6 alkyl), -N-$(C_1$-C_6 alkyl$)_2$, pyridinyl, thienyl, furyl, pyrrolyl, phenyl, -O-phenyl, benzyl, -O-benzyl, adamantyl, or morpholinyl, the rings of these groups being optionally substituted by from

1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NH_2$, $-NO_2$, $-CF_3$, or -OH;

R_2 is selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_{10} alkyl, preferably $-C_1$-C_6 alkyl, C_1-C_{10} alkoxy, preferably C_1-C_6 alkoxy, -CHO, -CN, $-NO_2$, $-NH_2$, -NH-C_1-C_6 alkyl, -N(C_1-C_6 alkyl)$_2$,
-N-SO_2-C_1-C_6 alkyl, or -SO_2-C_1-C_6 alkyl;

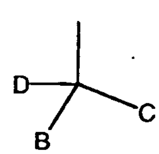
R_3 is selected from the group of C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, $-(CH_2)_n$-C_3-C_6 cycloalkyl, $-(CH_2)_n$-S-$(CH_2)_n$-C_3-C_6 cycloalkyl, or the groups of:

a) $-(CH_2)_n$-phenyl-O-phenyl, $-(CH_2)_n$-phenyl-CH_2-phenyl, $-(CH_2)_n$-O-phenyl-CH_2-phenyl, $-(CH_2)_n$-phenyl-(O-CH_2-phenyl)$_2$, $-CH_2$-phenyl-C(O)-benzothiazole or a moiety of the formulae:



wherein n is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2, Y is C_3-C_6 cycloalkyl, phenyl, benzyl, napthyl, pyridinyl, quinolyl, furyl, thienyl or pyrrolyl; rings of these groups being optionally substituted by from 1 to 3 substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NH_2$, $-NO_2$ or a five membered heterocyclic ring containing one heteroatom selected from N, S, or O, preferably S or O; or

b) a moiety of the formulae $-(CH_2)_n$-A, $-(CH_2)_n$-S-A, or $-(CH_2)_n$-O-A, wherein A is the moiety:

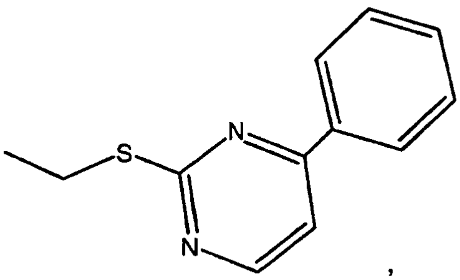


wherein

D is H, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, or -CF_3;

B and C are independently selected from phenyl, pyridinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, preferably 1 to 2, substituents selected from H, halogen, -CF_3, -OH, -C_1-C_6 alkyl, C_1-C_6 alkoxy, or -NO_2; or

c) a moiety of the formulae:



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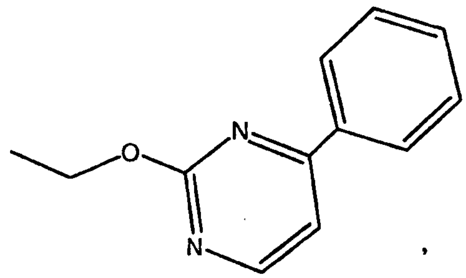

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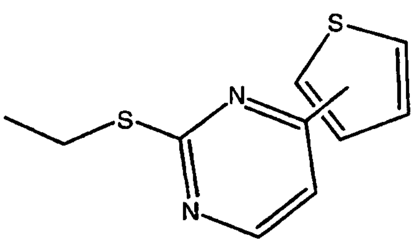

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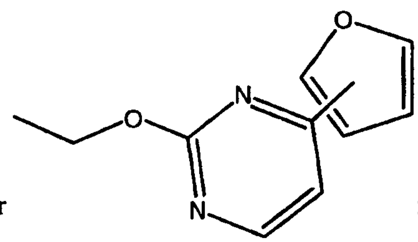
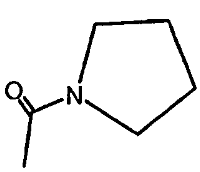


;

wherein the phenyl and pyrimidinyl rings of each moiety are optionally and independently substituted by from 1 to 3 substituents selected from halogen, -CF_3, -OH, -C_1-C_6 alkyl, C_1-C_6 alkoxy, or -NO_2;

R_4 is selected from H, halogen, -CF_3, -OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, benzyl, benzyloxy, phenyl, phenyloxy, -C(O)-phenyl, -C(O)-benzyl, -CH_2-(C_3-C_6 cycloalky), -C(O)-OH, -CH=O, -C(O)-C_1-C_6 alkyl, -C(O)-O-C_1-C_6 alkyl, -C(O)-CF_3, -$(CH_2)_n$-S-CH_2-(C_3-C_6 cycloalky),



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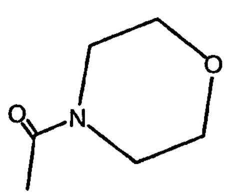

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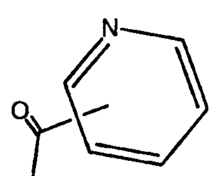
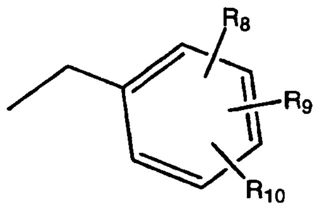


;

the phenyl and benzyl rings of the relevant R_3 groups being optionally substituted by from 1 to 3 groups selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, -C(O)-OH, or -OH;

n is an integer from 0 to 3;

R_5 is selected from -COOH, -C(O)-COOH, $-(CH_2)_n$-C(O)-COOH, $-(CH_2)_n$-COOH, -CH=CH-COOH,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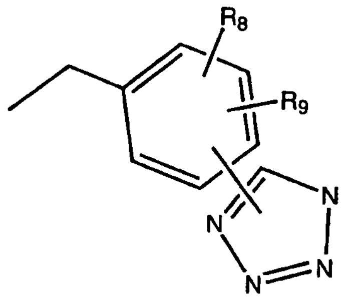
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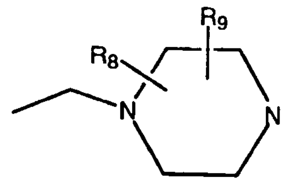
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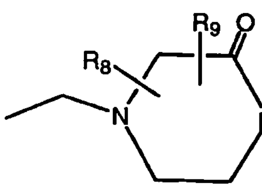
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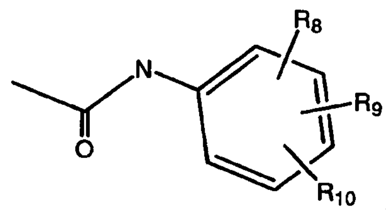
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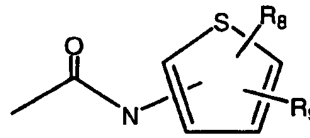
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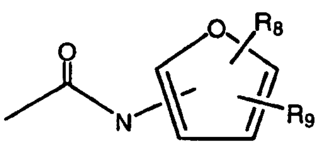
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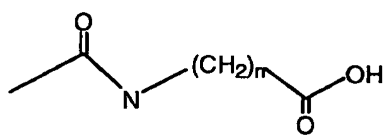
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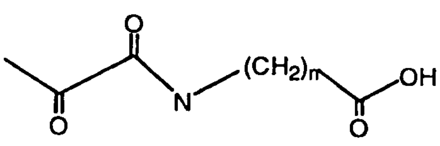
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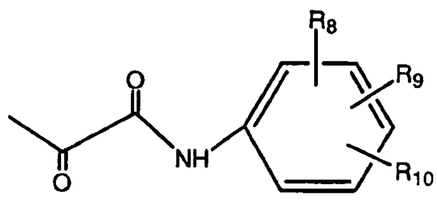
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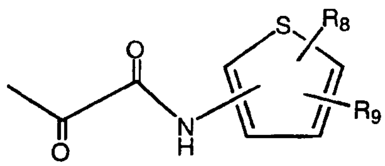
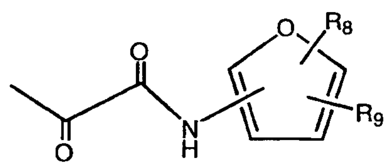
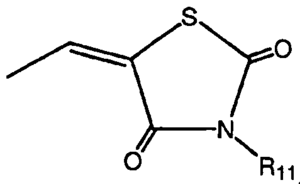
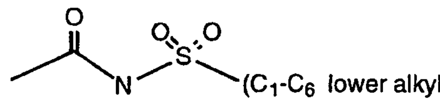
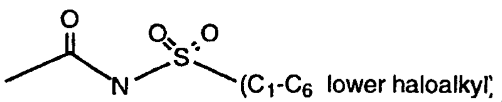
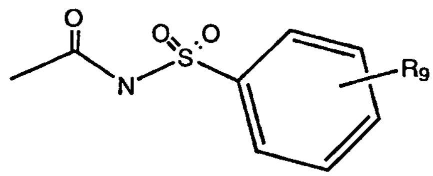
, , or

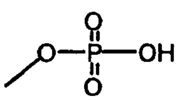
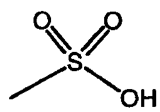






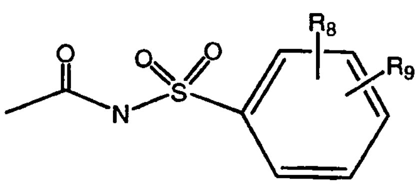
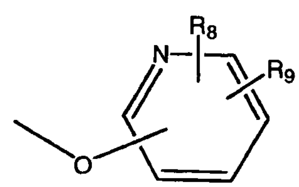
 ;

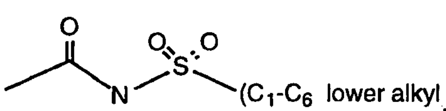
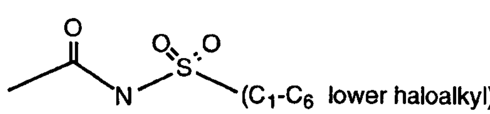
R_8 is selected from H, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, tetrazole,

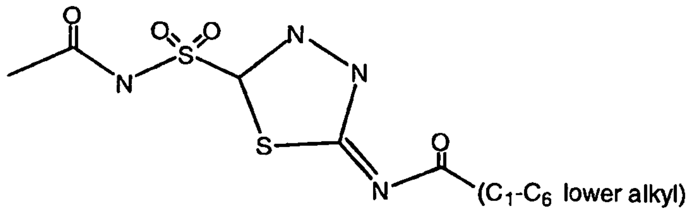
, or ;

R_9 is selected from H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl$)_2$;

R_{10} is selected from the group of H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl$)_2$,

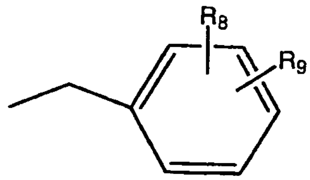
, ,

,  or

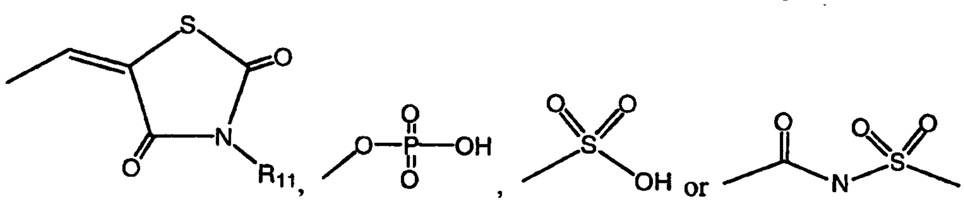


;

R_{11} is selected from H, C_1-C_6 lower alkyl, $-CF_3$, -COOH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH, or


;

with a proviso that the complete moiety at the indole or indoline 1-position created by any combination of R_5, R_8, R_9, R_{10}, and/or R_{11} shall contain at least one acidic moiety selected from or containing a carboxylic acid, a tetrazole, or a moiety of the formulae: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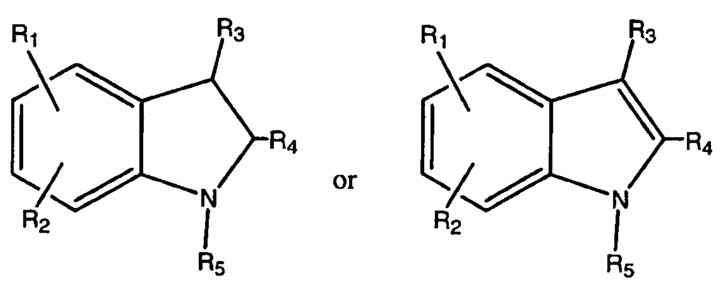
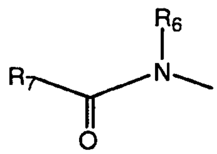
or a pharmaceutically acceptable salt thereof.

Another group of compounds of this invention have the following formulae:



wherein:

R_1 is selected form H, halogen, $-CF_3$, -OH, $-C_1-C_6$ alkyl, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, phenyl, -O-phenyl, benzyl, -O-benzyl, -S-benzyl or a moiety of the formulae: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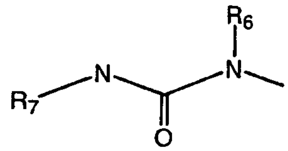
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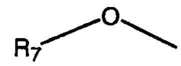
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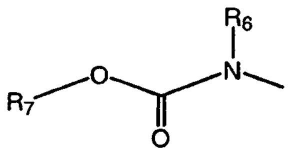
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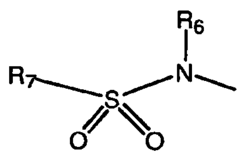
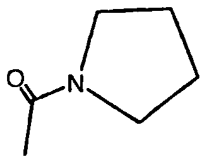
or  ;

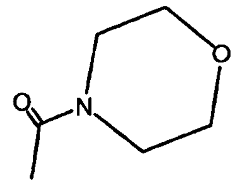
R_6 is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, -O-phenyl, benzyl, -O-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

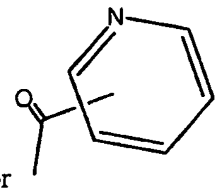
R_7 is selected from $-(CH_2)_n$-COOH, $-(CH_2)_n-N-(C_1-C_6\ alkyl)_2$, $-(CH_2)_n-NH-(C_1-C_6$ alkyl), $-CF_3$, C_1-C_6 alkyl, C_3-C_5 cycloalkyl, C_1-C_6 alkoxy, $-NH-(C_1-C_6$ alkyl), $-N-(C_1-C_6\ alkyl)_2$, pyridinyl, thienyl, furyl, pyrrolyl, phenyl, -O-phenyl, benzyl, -O-benzyl, adamantyl, or morpholinyl, the pyridinyl, phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

R_2 is selected from H, halogen, $-CF_3$, -OH, $-C_1-C_{10}$ alkyl, preferably $-C_1-C_6$ alkyl, C_1-C_{10} alkoxy, preferably C_1-C_6 alkoxy, -CHO, -CN, $-NO_2$, $-NH_2$, $-NH-C_1-C_6$ alkyl, $-N(C_1-C_6\ alkyl)_2$, $-N-SO_2-C_1-C_6$ alkyl, or $-SO_2-C_1-C_6$ alkyl;

R_3 is selected from H, halogen, $-CF_3$, -OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, benzyl, benzyloxy, phenyl, phenyloxy, -C(O)-phenyl, -C(O)-benzyl, $-CH_2-(C_3-C_5$ cycloalky), -C(O)-OH, -CH=O, $-C(O)-C_1-C_6$ alkyl, $-C(O)-O-C_1-C_6$ alkyl, $-C(O)-CF_3$, $-(CH_2)_n-S-CH_2-(C_3-C_5$ cycloalky),



, 

, or 

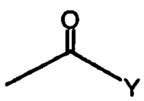
;

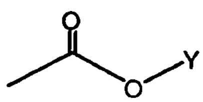
the phenyl and benzyl rings of the relevant R_3 groups being optionally substituted by from 1 to 3 groups selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, -C(O)-OH, or -OH;

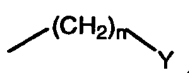
n is an integer from 0 to 3;

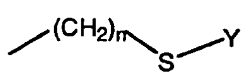
R_4 is selected from the group of C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, $-(CH_2)_n$-C_3-C_5 cycloalkyl, $-(CH_2)_n$-S-$(CH_2)_n$-C_3-C_5 cycloalkyl, $-(CH_2)_n$-O-$(CH_2)_n$-C_3-C_5 cycloalkyl, or the groups of:

a) $-(CH_2)_n$-phenyl-O-phenyl, $-(CH_2)_n$-phenyl-CH_2-phenyl, $-(CH_2)_n$-O-phenyl-CH_2-phenyl, $-(CH_2)_n$-phenyl-(O-CH_2-phenyl$)_2$, $-CH_2$-phenyl-C(O)-benzothiazole or a moiety of the formulae:



, 

, 

, 

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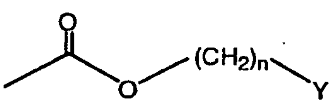
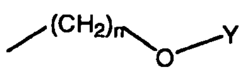
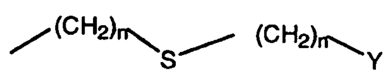


, 

, 

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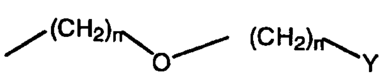
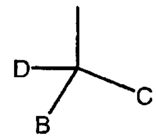


,

wherein n is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2, Y is C_3-C_6 cycloalkyl, phenyl, benzyl, napthyl, pyridinyl, quinolyl, furyl, thienyl or pyrrolyl; rings of these groups being optionally substituted by from 1 to 3 substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$ or a five membered heterocyclic ring containing one heteroatom selected from N, S, or O, preferably S or O; or

b) a moiety of the formulae $-(CH_2)_n$-A, $-(CH_2)_n$-S-A, or $-(CH_2)_n$-O-A, wherein A is the moiety:

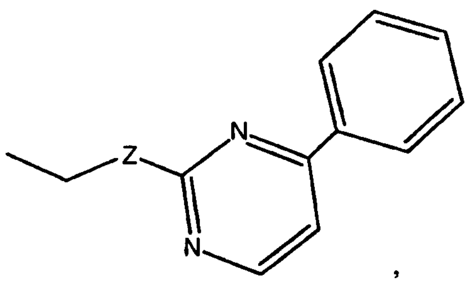


wherein

D is H, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, or $-CF_3$;

B and C are independently selected from phenyl, pyridinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, preferably 1 to 2, substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, or $-NO_2$; or

c) a moiety of the formulae:



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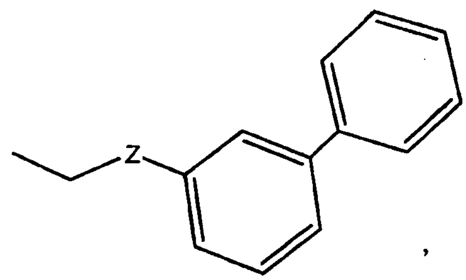

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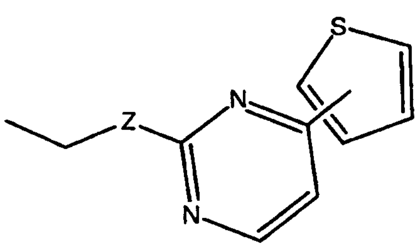

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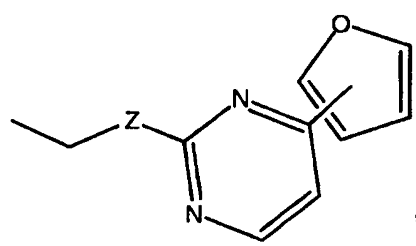

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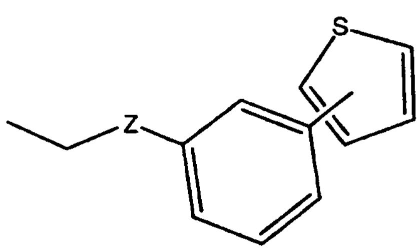

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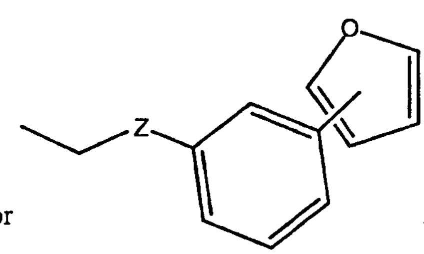
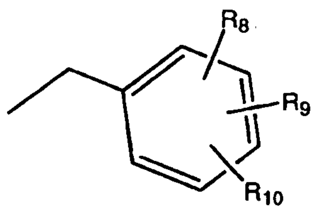
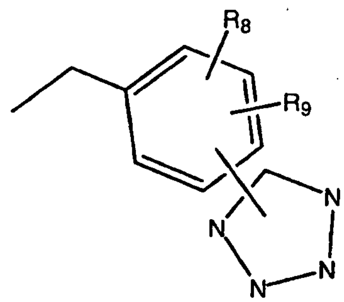
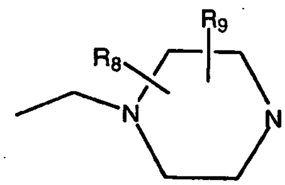
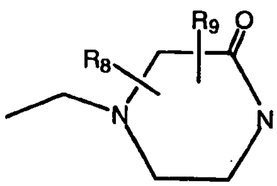
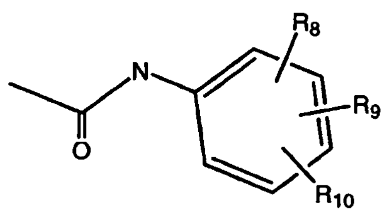
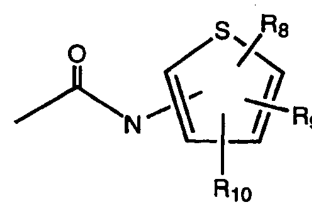


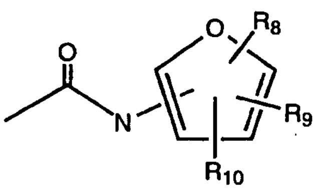
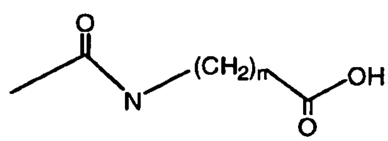
;

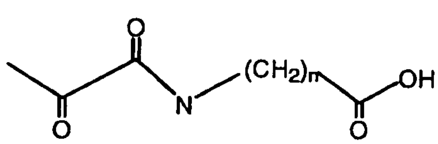
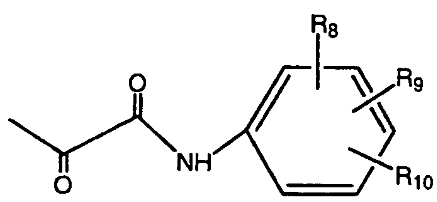
wherein Z is O or S and the phenyl and pyrimidinyl rings of each moiety are optionally and independently substituted by from 1 to 3 substituents selected from halogen, $-CF_3$, $-OH$, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, or $-NO_2$;

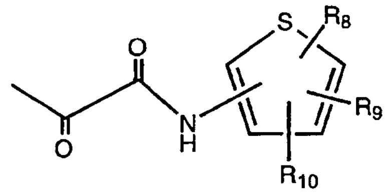
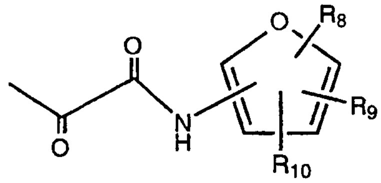
R_5 is selected from -COOH, -C(O)-COOH, $-(CH_2)_n$-C(O)-COOH, $-(CH_2)_n$-COOH, -CH=CH-COOH,

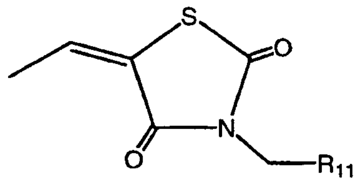
 ,  ,  ,

 ,  ,  ,

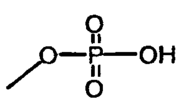
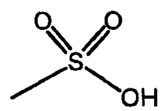
 ,  ,

 ,  ,

, , or

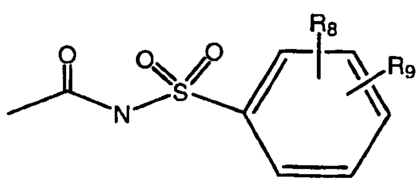
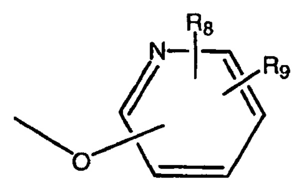
 ;

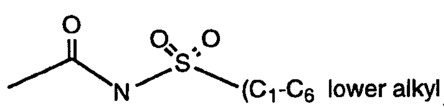
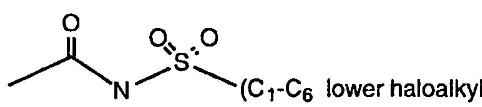
R_8 is selected from H, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, tetrazole,

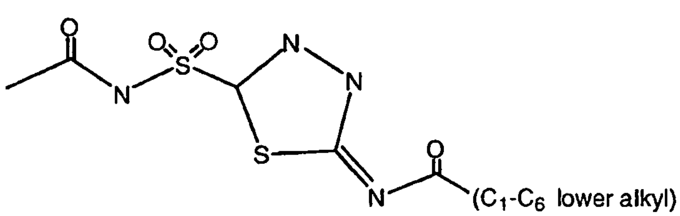
, or ;

R_9 is selected from H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$;

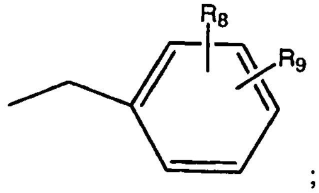
R_{10} is selected from the group of H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$,

, ,

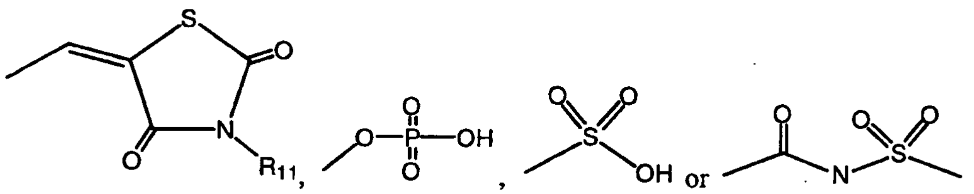
,  or

 ;

R_{11} is selected from H, C_1-C_6 lower alkyl, $-CF_3$, -COOH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH, or



with a proviso that the complete moiety at the indole or indoline 1-position created by any combination of R_5, R_8, R_9, R_{10}, and/or R_{11} shall contain at least one acidic moiety selected from or containing a carboxylic acid, a tetrazole, or a moiety of the formulae:



or a pharmaceutically acceptable salt thereof.

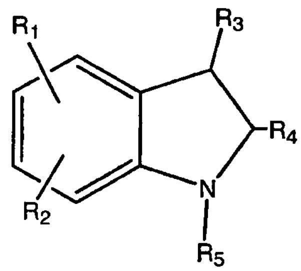
One group of compounds within this invention are those in which the indole or indoline 3-position (R_3) is substituted only by hydrogen and the substituents at the other indole or indoline positions are as described above.

Another group of this invention comprises compounds in which R_2 is hydrogen and the groups at R_1, R_3, and R_5 are as defined above. Within this group are two further preferred groups. In the first, R_1 is in the indole or indoline 5 position and in the second R_1 is in the indole or indoline 6 position.

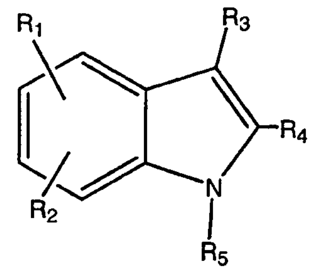
In a further preferred group herein, R_1 is in the indole or indoline 5-position and is benzyloxy, R_2 and R_4 are hydrogen and R_3 and R_5 are as defined above.

It is also understood that there is a further preferred subgroup within each of the groups set forth herein wherein the core molecule is an indole moiety, rather than an indoline. There is also understood to be a second group within each wherein the core molecule is an indoline moiety.

Another subset of compounds of this invention have the following formulae:

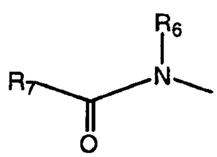


or



wherein:

R_1 is selected form H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, phenyl, -O-phenyl, benzyl, -O-benzyl, or a moiety of the formulae:



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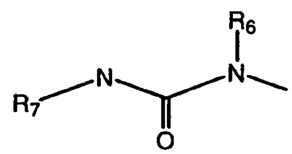

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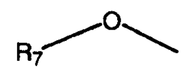

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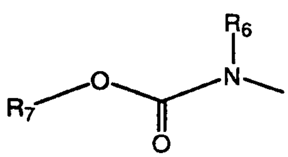

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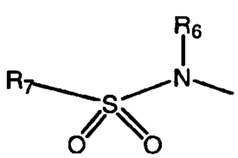
or



;

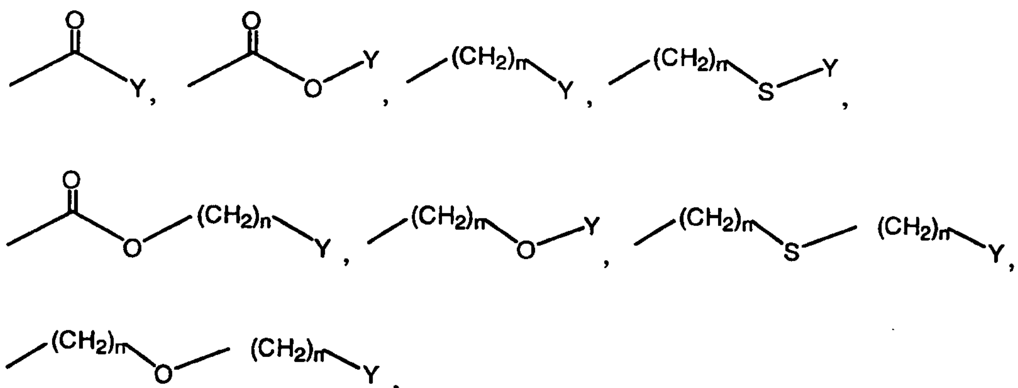
R_6 is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, -O-phenyl, benzyl, -O-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

R_7 is selected from $-(CH_2)_n$-COOH, $-(CH_2)_n$-N-(C_1-C_6 alkyl$)_2$, $-(CH_2)_n$-NH-(C_1-C_6 alkyl), $-CF_3$, C_1-C_6 alkyl, C_3-C_5 cycloalkyl, C_1-C_6 alkoxy, -NH-(C_1-C_6 alkyl), -N-(C_1-C_6 alkyl$)_2$, pyridinyl, thienyl, furyl, pyrrolyl, phenyl, -O-phenyl, benzyl, -O-benzyl, adamantyl, or morpholinyl, the pyridinyl, phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

R_2 is selected from H, halogen, $-CF_3$, -OH, $-C_1-C_{10}$ alkyl, preferably $-C_1-C_6$ alkyl, C_1-C_{10} alkoxy, preferably C_1-C_6 alkoxy, -CHO, -CN, $-NO_2$, $-NH_2$, $-NH-C_1-C_6$ alkyl, $-N(C_1-C_6\ alkyl)_2$, $-N-SO_2-C_1-C_6$ alkyl, or $-SO_2-C_1-C_6$ alkyl;

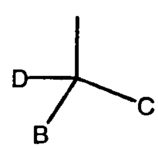
R_3 is selected from the group of C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, $-(CH_2)_n-C_3-C_6$ cycloalkyl, $-(CH_2)_n-S-(CH_2)_n-C_3-C_5$ cycloalkyl, or the groups of:

a) $-(CH_2)_n$-phenyl-O-phenyl, $-(CH_2)_n$-phenyl-CH_2-phenyl, $-(CH_2)_n$-O-phenyl-CH_2-phenyl, $-(CH_2)_n$-phenyl-(O-CH_2-phenyl$)_2$, $-CH_2$-phenyl-C(O)-benzothiazole or a moiety of the formulae:



wherein n is an integer from 0 to 3, preferably 1 to 3, more preferably 1 to 2, Y is C_3-C_5 cycloalkyl, phenyl, benzyl, napthyl, pyridinyl, quinolyl, furyl, thienyl or pyrrolyl; rings of these groups being optionally substituted by from 1 to 3 substituents selected from H, halogen, $-CF_3$, -OH, $-C_1-C_6$ alkyl, C_1-C_6 alkoxy, $-NO_2$ or a five membered heterocyclic ring containing one heteroatom selected from N, S, or O, preferably S or O; or

b) a moiety of the formulae $-(CH_2)_n$-A, $-(CH_2)_n$-S-A, or $-(CH_2)_n$-O-A, wherein A is the moiety:

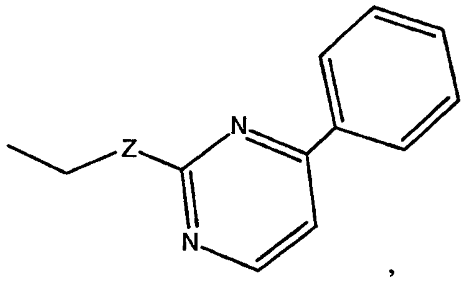


wherein

D is H, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, or $-CF_3$;

B and C are independently selected from phenyl, pyridinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, preferably 1 to 2, substituents selected from H, halogen, $-CF_3$, -OH, $-C_1-C_6$ alkyl, C_1-C_6 alkoxy, $-NH_2$ or $-NO_2$; or

c) a moiety of the formulae:



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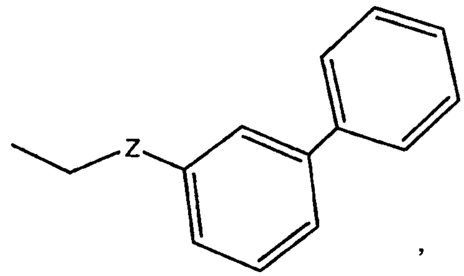

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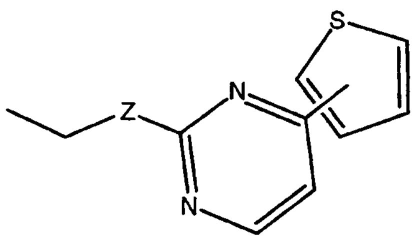

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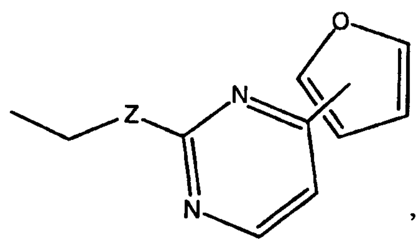

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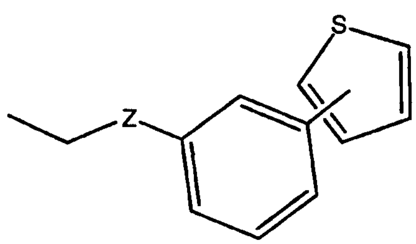

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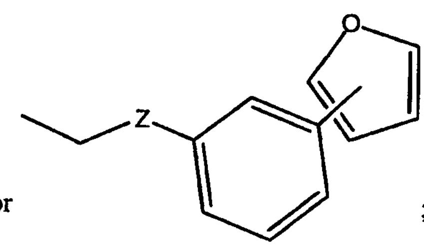
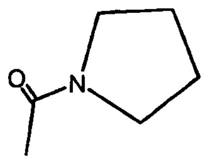
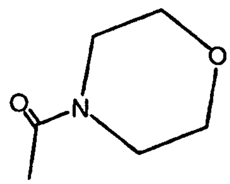
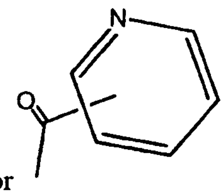


;

wherein Z is O or S and the phenyl and pyrimidinyl rings of each moiety are optionally and independently substituted by from 1 to 3 substituents selected from halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, or $-NO_2$, $-NH_2$;

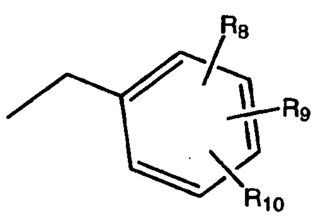
R_4 is selected from H, halogen, $-CF_3$, -OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, benzyl, benzyloxy, phenyl, phenyloxy, -C(O)-phenyl, -C(O)-benzyl, $-CH_2$-(C_3-C_5 cycloalky), -C(O)-OH, -CH=O, -C(O)-C_1-C_6 alkyl, -C(O)-O-C_1-C_6 alkyl, -C(O)-CF_3, $-(CH_2)_n$-S-CH_2-(C_3-C_5 cycloalky),

, , or ;

the phenyl and benzyl rings of the relevant R_3 groups being optionally substituted by from 1 to 3 groups selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, -C(O)-OH, or -OH;

n is an integer from 0 to 3;

R_5 is selected from -COOH, -C(O)-COOH, $-(CH_2)_n$-C(O)-COOH, $-(CH_2)_n$-COOH, -CH=CH-COOH,



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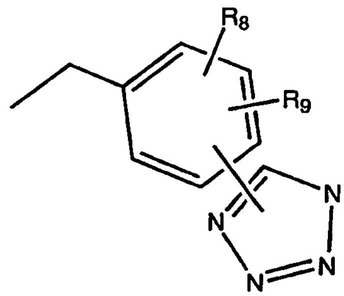

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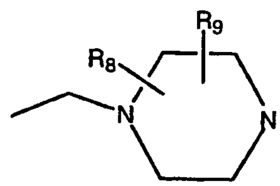

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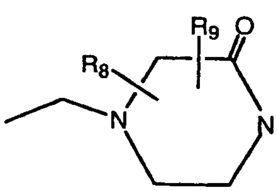

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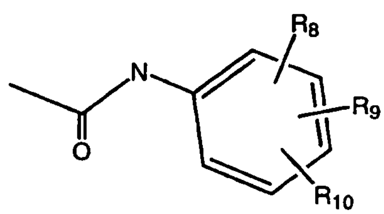

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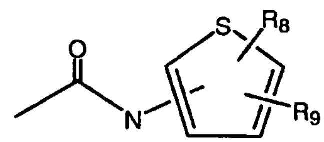

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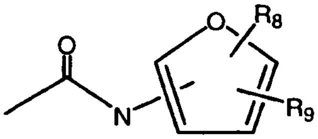

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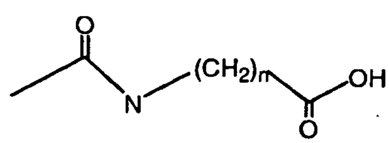

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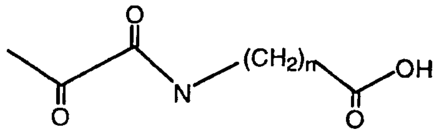
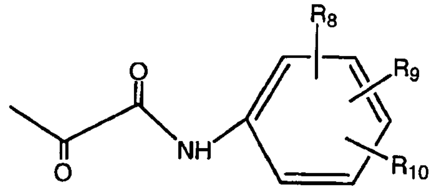


, 

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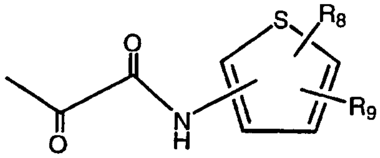
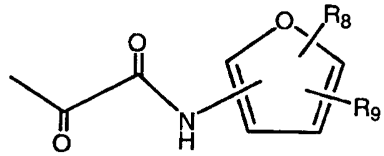


, 

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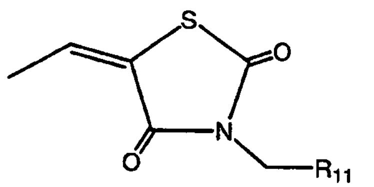
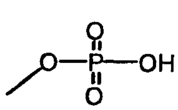
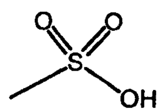


;

R_8 is selected from H, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, tetrazole,

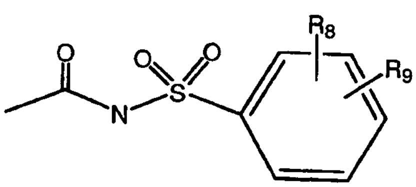


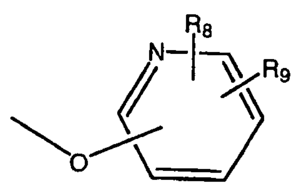
, or 

;

R_9 is selected from H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl$)_2$;

R_{10} is selected from the group of H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl$)_2$,



, 

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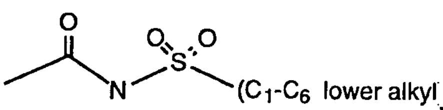
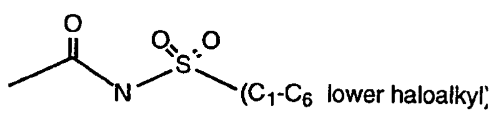


, 

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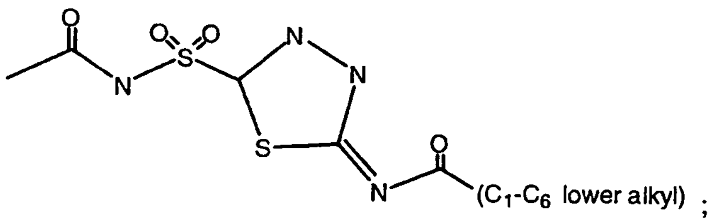
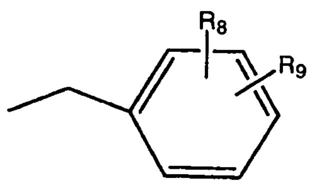
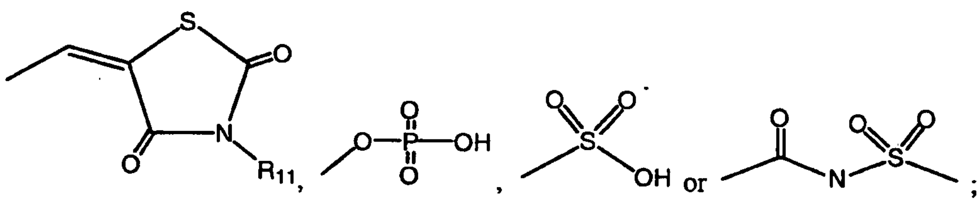


R_{11} is selected from H, C_1-C_6 lower alkyl, $-CF_3$, -COOH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH, or



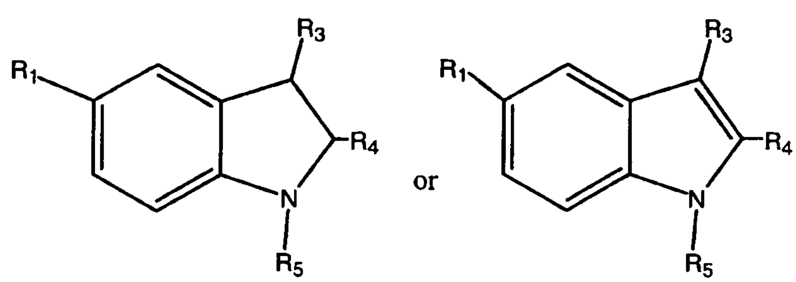
;

with a proviso that the complete moiety at the indole or indoline 1-position created by any combination of R_5, R_8, R_9, R_{10}, and/or R_{11} shall contain at least one acidic moiety selected from or containing a carboxylic acid, a tetrazole, or a moiety of the formulae:



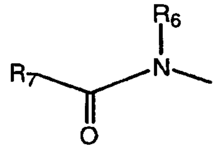
or a pharmaceutically acceptable salt thereof.

Further preferred among the compounds of this invention are those having the formulae:



wherein:

R_1 is selected form $-NH_2$, -O-phenyl, benzyl, -O-benzyl, -N-benzyl, -N-benzyl-O-phenyl, -S-benzyl or a moiety of the formulae: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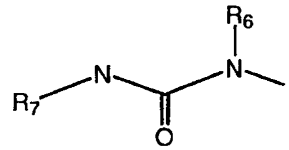
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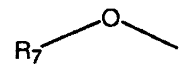
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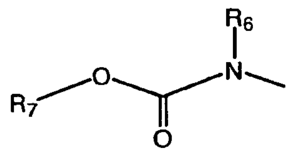
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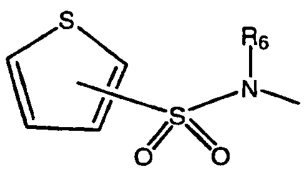
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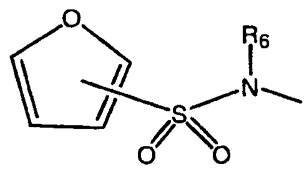
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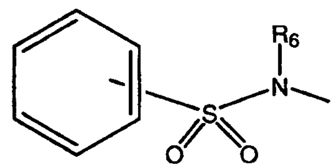
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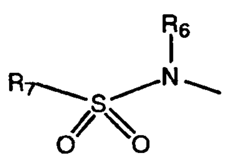
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R_6 is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, -O-phenyl, benzyl, -O-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

R_7 is selected from $-(CH_2)_n$-COOH, $-(CH_2)_n$-N-(C_1-C_6 alkyl)$_2$, $-(CH_2)_n$-NH-(C_1-C_6 alkyl), $-CF_3$, C_1-C_6 alkyl, C_3-C_5 cycloalkyl, C_1-C_6 alkoxy, -NH-(C_1-C_6 alkyl), -N-(C_1-C_6 alkyl)$_2$, pyridinyl, thienyl, furyl, pyrrolyl, phenyl, -O-phenyl, benzyl, -O-benzyl, adamantyl, or morpholinyl, the rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

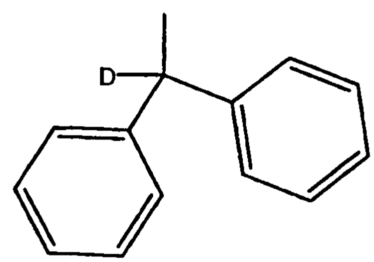
n is an integer from 0 to 3;

R_3 is selected from halogen, $-C_1$-C_6 alkyl, $-C_1$-C_6 alkoxy, $-CF_3$, -CH=O, -C(O)-C_1-C_6 alkyl, -C(O)-O-C_1-C_6 alkyl, -C(O)-OH, -C(O)-CF_3, -C(O)-phenyl, -C(O)-benzyl, -C(O)-pyrrolyl, -C(O)-thienyl, -C(O)-furanyl, or -C(O)-morpholinyl;

R_4 is selected from the group of -$(CH_2)_n$-C_3-C_6 cycloalkyl, -$(CH_2)_n$-S-$(CH_2)_n$-C_3-C_6 cycloalkyl, -$(CH_2)_n$-O-$(CH_2)_n$-C_3-C_6 cycloalkyl, -$(CH_2)_n$-S-C_1-C_6 alkyl, the groups of:

a) -C(O)-O-$(CH_2)_n$-C_3-C_5 cycloalkyl, -$(CH_2)_n$-phenyl, -$(CH_2)_n$-O-phenyl, -$(CH_2)_n$-S-phenyl, -$(CH_2)_n$-S-$(CH_2)_n$-phenyl, -$(CH_2)_n$-phenyl-O-phenyl, -$(CH_2)_n$-phenyl-CH_2-phenyl, -$(CH_2)_n$-O-phenyl-CH_2-phenyl, -$(CH_2)_n$-phenyl-(O-CH_2-phenyl$)_2$, -C(O)-O-phenyl, -C(O)-O-benzyl, -C(O)-O-pyridinyl, -C(O)-O-napthyl, -$(CH_2)_n$-S-napthyl, -$(CH_2)_n$-S-pyridinyl, -$(CH_2)_n$-pyridinyl or -$(CH_2)_n$-napthyl, -$(CH_2)_n$-O-napthyl, the phenyl, pyridinyl and napthyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$ or a five membered heterocyclic ring containing one heteroatom selected from N, S, or O, preferably S or O; or

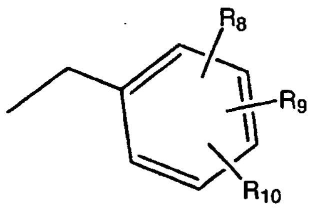
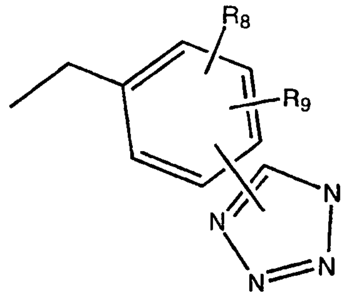
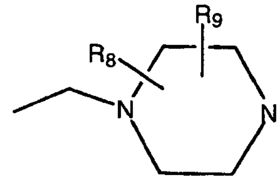
b) a moiety of the formulae -$(CH_2)_n$-A, -$(CH_2)_n$-S-A, or -$(CH_2)_n$-O-A, wherein A is the moiety:

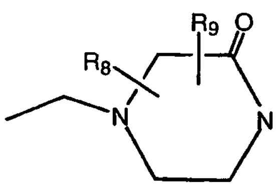
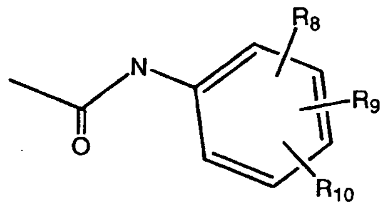
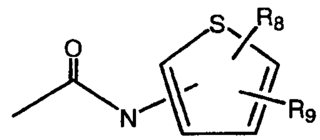


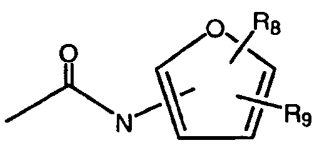
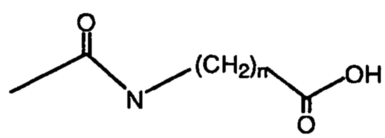
wherein

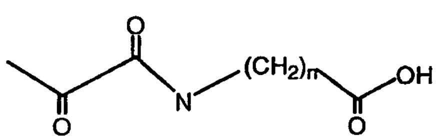
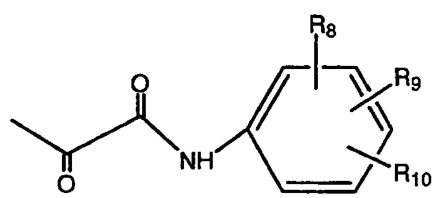
D is H, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, or $-CF_3$;

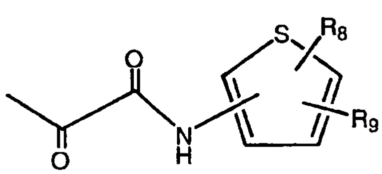
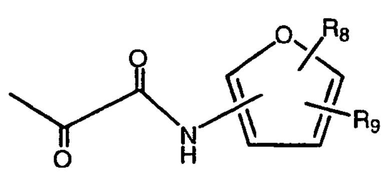
R_5 is selected from -COOH, -C(O)-COOH, -$(CH_2)_n$-C(O)-COOH, -$(CH_2)_n$-COOH, -CH=CH-COOH,

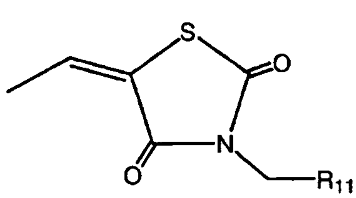
 ,  ,  ,

 ,  ,  ,

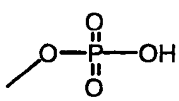
 ,  ,

 ,  ,

 ,  , or

 ;

R_8 is selected from H, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, tetrazole,



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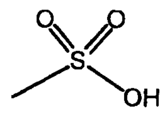

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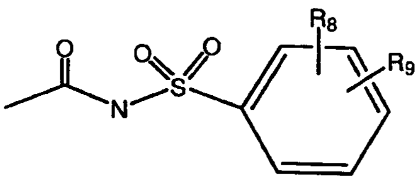
R_9 is selected from H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$;

R_{10} is selected from the group of H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$,



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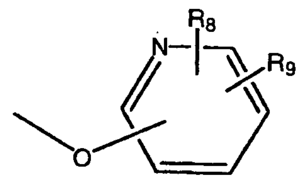

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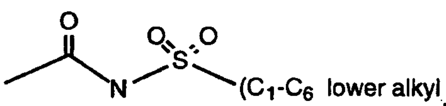

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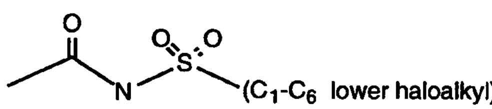

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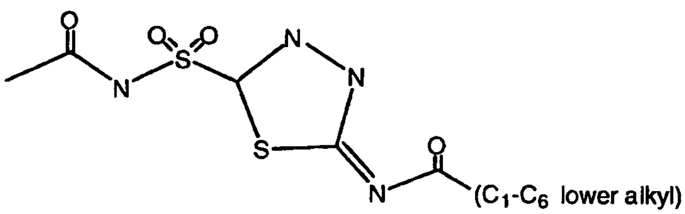

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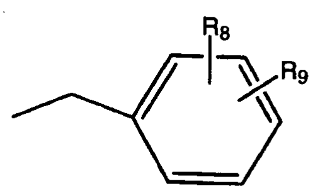
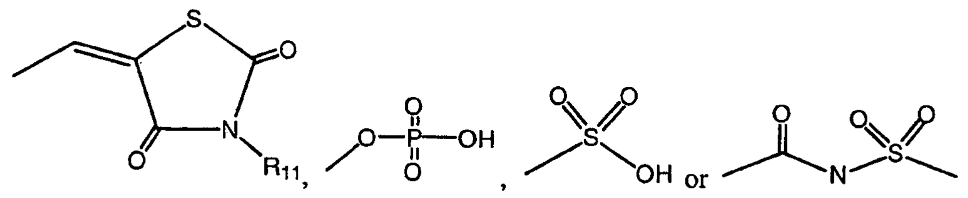
R_{11} is selected from H, C_1-C_6 lower alkyl, -CF_3, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, or



;

with a proviso that the complete moiety at the indole or indoline 1-position created by any combination of R_5, R_8, R_9, R_{10}, and/or R_{11} shall contain at least one acidic moiety selected from or containing a carboxylic acid, a tetrazole, or a moiety of the formulae:



or a pharmaceutically acceptable salt thereof.

Detailed Description of Preferred Embodiments

As used herein, the terms "aryl" and "substituted aryl" are understood to include monocyclic, particularly including five- and six-membered monocyclic, aromatic and heteroaromatic ring moieties and bicyclic aromatic and heteroaromatic ring moieties, particularly including those having from 9 to 10 ring atoms. Among these aryl groups are understood to be phenyl rings, including those found in phenoxy, benzyl, benzyloxy, biphenyl and other such moieties. The aryl and heteroaryl groups of this invention also include the following:

a) a five-membered heterocyclic ring containing one or two ring heteroatoms selected from N, S or O including, but not limited to, furan, pyrrole, thiophene, imidazole, pyrazole, isothiazole, isoxazole, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazole, pyrazoline, imidazole, tetrazole, or oxathiazole; or

b) a six-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, S or O including, but not limited to, pyran, pyridine, pyrazine, pyrimidine, pyridazine, piperidine, piperazine, tetrazine, thiazine, thiadizine, oxazine, or morpholine; or

c) a bicyclic ring moiety optionally containing from 1 to 3 ring heteroatoms selected from N, S or O including, but not limited to benzofuran, chromene, indole, isoindole, indoline, isoindoline, napthalene, purine, indolizine, indazole, quinoline, isoquinoline, quinolizine, quinazoline, cinnoline, phthalazine, or napthyridine.

The "substituted aryl" groups of this invention include such moieties being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_{10} alkyl, preferably C_1-C_6 alkyl, C_1-C_{10} alkoxy, preferably C_1-C_6 alkoxy, -CHO, -COOH or esters thereof, -

NO_2, $-NH_2$, -CN, $-CF_3$ or -OH or combinations thereof, such as $-CH_2CF_3$, $-NH(CH_3)$, etc.

A preferred subset of these groups, optionally substituted as just described, include moieties formed from benzene, pyridine, napthylene or quinoline rings. A further preferred group includes those of furan, pyrrole, thiophene, pyrimidine, and morpholine rings. A preferred group of bicyclic aromatic groups includes benzofuran, indole, napthalene, and quinoline rings.

The alkyl, alkenyl and alkinyl groups referred to herein indicate such groups having from 1 to 10, preferably 1 to 6 carbon atoms, and may be straight, branched or cyclic. Unless indicated otherwise, it is preferred that these groups be straight or branched. Halogens herein are understood to include F, Cl, Br and I.

As used herein, "phospholipase enzyme activity" means positive activity in an assay for metabolism of phospholipids (preferably one of the assays described in Example 86 below). A compound has "phospholipase enzyme inhibiting activity" when it inhibits the activity of a phospholipase (preferably $cPLA_2$) in any available assay (preferably an assay described below in Example 86 or Example 87) for enzyme activity. In preferred embodiments, a compound has (1) an IC_{50} value of less than about 25 μM, preferably less than about 6 μM, in the LysoPC assay; (2) an IC_{50} value of less than about 50 μM in the vesicle assay; (3) an IC_{50} value of less than about 1 μM in the PMN assay; (4) an IC_{50} value of less than about 15 μM in the Coumarine assay; and/or (5) measurable activity (preferably at least about 5% reduction in edema, more preferably at least about 10% reduction, more preferably at least about 15%, most preferably 20-30%) in the rat carrageenan-induced footpad edema test.

Compounds of the present invention are useful for inhibiting phospholipase enzyme (preferably $cPLA_2$) activity and, therefore, are useful in "treating" (i.e., treating, preventing or ameliorating) inflammatory or inflammation-related responses or conditions (e.g., rheumatoid arthritis, psoriasis, asthma, inflammatory bowel disease, and other diseases mediated by prostaglandins, leukotrienes or PAF) and other conditions, such as osteoporosis, colitis, myelogenous leukemia, diabetes, wasting and atherosclerosis.

The present invention encompasses both pharmaceutical compositions and therapeutic methods of treatment or use which employ compounds of the present invention.

Compounds of the present invention may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to a compound or compounds of the present invention and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in

the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition may further contain other anti-inflammatory agents. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with compounds of the present invention, or to minimize side effects caused by the compound of the present invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which compounds of the present invention are combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of an inflammatory response or condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of a compound of the present invention is administered to a mammal having a condition to be treated. Compounds of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing other anti-inflammatory agents, cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more other anti-inflammatory agents, cytokines, lymphokines or other hematopoietic factors, compounds of the present invention may be administered either simultaneously with the other anti-inflammatory agent(s), cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering compounds of the present invention in combination with other anti-

inflammatory agent(s), cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of compounds of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, or cutaneous, subcutaneous, or intravenous injection.

When a therapeutically effective amount of compounds of the present invention is administered orally, compounds of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% compound of the present invention, and preferably from about 25 to 90% compound of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of compound of the present invention, and preferably from about 1 to 50% compound of the present invention.

When a therapeutically effective amount of compounds of the present invention is administered by intravenous, cutaneous or subcutaneous injection, compounds of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to compounds of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of compound(s) of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of compound of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of compound of the present invention and observe the patient's response. Larger

doses of compounds of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.1 μg to about 100 mg (preferably about .1 mg to about 50 mg, more preferably about 1 mg to about 2 mg) of compound of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the compounds of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Compounds of the present invention invention can be made according to the methods and examples described below. Synthesis of preferred compounds of the present invention are described in the examples below.

Method A

Ethyl 5-nitro-2-carboxylate indole is chlorinated in the 3-position by the agency of N-chlorosuccinamide in a solvent such as DMF or DMSO at an elevated temperature of 40 °C - 80 °C. The ester is then reduced in a three step procedure. First the ester is hydrolysed under basic conditions with a base such as sodium hydroxide or potassium hydroxide in a solvent system such as water:methanol:THF. The acid is then activated by he addition of carbonyl diimidizole in THF and reduced with a reducing agent such as sodium borohydride or sodium triacetoxyborohydride in an alcoholic solvent system such as methanol or ethanol. The resulting alcohol is protected as the TBDMS ether with TBDMSCl in a solvent such as DMF, methylene chloride or THF with a base such a triethylamine or imidazole. The indole nitrogen is then alkylated with methyl 4-bromomethlybenzoate in a solvent such as THF, acetonitrile or DMF with a base such as sodium hydride, *n*-BuLi or potassium bis(trimethylsilyl)amide. The 5-nitro group is then reduced by exposure to H_2 in the presence of a catalyst such as Pt/C or Pd/C in a solvent such as ethyl acetate, methanol or THF or a mixture of two or all of the three. The amine is then acylated with cyclopentylcarbonyl chloride in a biphasic system of saturated sodium bicarbonate and methylene chloride. R1 is then introduced in a two step procedure wherein the TBDMS ether is converted to a bromide by exposure to

dibromotriphenylphosphorane in methylene chloride and then the crude bromide is displaced by a variety of thiols or phenols in a solvent such as THF, methylene chloride or DMF in the presence of a base such as potassium carbonate or cesium carbonate. The product esters are then prepared by the hydrolysis of the ester under basic conditions with sodium hydroxide in a solvent system such as water:MeOH:THF.

Method B

Acylation at the 3-position of indole **I** with an acylating agent such as naphthoyl chloride could be accomplished using ethylmagnesium bromide in a solvent such as THF to give **II**. Alkylation of the indole nitrogen could be accomplished by exposure to a suitable base such as sodium hydride followed by treatment with the appropriate. Deprotection of the hydroxy protecting group with tetrabutylammonium fluoride and oxidation with a suitable oxidizing agent provided **IV**. A Horner-Wittig reaction with trimethoxyphosphonoacetate in a suitable solvent such as tetrahydrofuran gave the unsaturated ester **V** which could be deprotected at the indole 1-position with a suitable reagent system such as hydrofluoric acid in acetonitrile. Saponification of the remaining acid group gave the compound **VI**

Method C

Indole I can be converted to II in two steps: (1) reduction with LAH in a solvent such as THF and (2) silylation with t-butyldimethylsilyl chloride (TBDMSCl) in a solvent such as dichloromethane or DMF in the presence of a base such as imidazole. Treatment of II with Grignard reagent such as ethyl magnesium bromide in a solvent such as THF at -60°C, acylation of the resulting magnesium salt with a suitable acyl chloride such as acetyl chloride in ether and finally, alkylation on the nitrogen with an alkyl halide such as methyl(4-bromomethyl)benzoate in the presence of a strong base such as NaH in DMF affords ketone III. The silyl group on III is removed using tetrabutylammonium fluoride in a solvent such as THF, the resulting alcohol is then converted to bromide using carbon tetrabromide and bis(diphenylphosphino)ethane in a solvent such as dichloromethane to yield bromide IV. Displacement of the bromine of IV with a thiol compound in the presence of a base such as cesium carbonate, or with an alcohol in the presence of a strong base such as NaH in DMF affords V (sulfide or ether respectively).

Method D

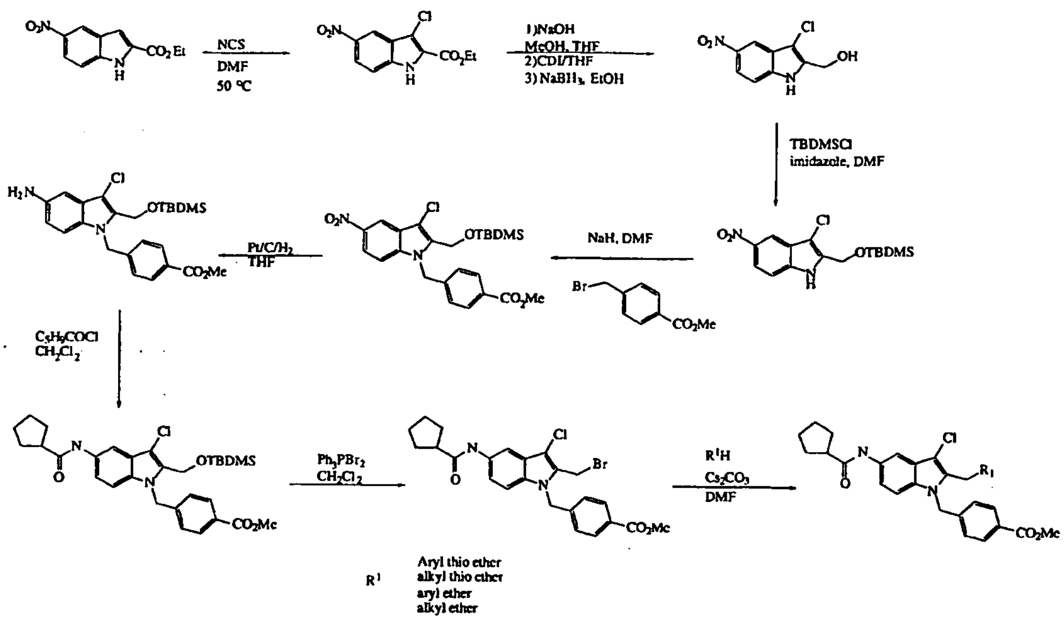
The protected alcohol was deprotected in a suitable solvent such as THF and the resulting alcohol was functionalized to a halide using carbon tetrabromide or methanesulfonyl chloride and then reacted with an oxygen nucleophile, coupled with prior

deprotonation with a strong base such as sodium hydride, or a sulfur nucleophile in the presence of cesium carbonate in DMF or THF. The nitro group could then be reduced to an amine via a Pt/carbon hydrogenation protocol or copper acetate sodium borohydride procedure. The resulting amine could be hydrolyzed,using a standard procedure of sodium hydroxide in THF/MeOH or coupled to a variety of acylating reagents, such as acid chlorides, chloroformates and isocyanates where the reactions are generally performed in the presence of a base in a solvent such as THF or dichloromethane. The amine could also be acylated via an EDCI coupling procedure with a variety of acids. The starting amine could also be alkylated by a reductive amination procedure using a varity of aldehydes and sodium triacetoxyborohydride as the reducing agent. These functionalized amines could be hydrolyzed to yield the desired acids which could also be converted to the acylsulfonamide by EDCI coupling with an sulfonamide. Alternatively, the functionalized amines could be alkylated further by reaction with a strong base and an alkyl halide and then hydrolyzed under the standard conditions to yield the requisite product.

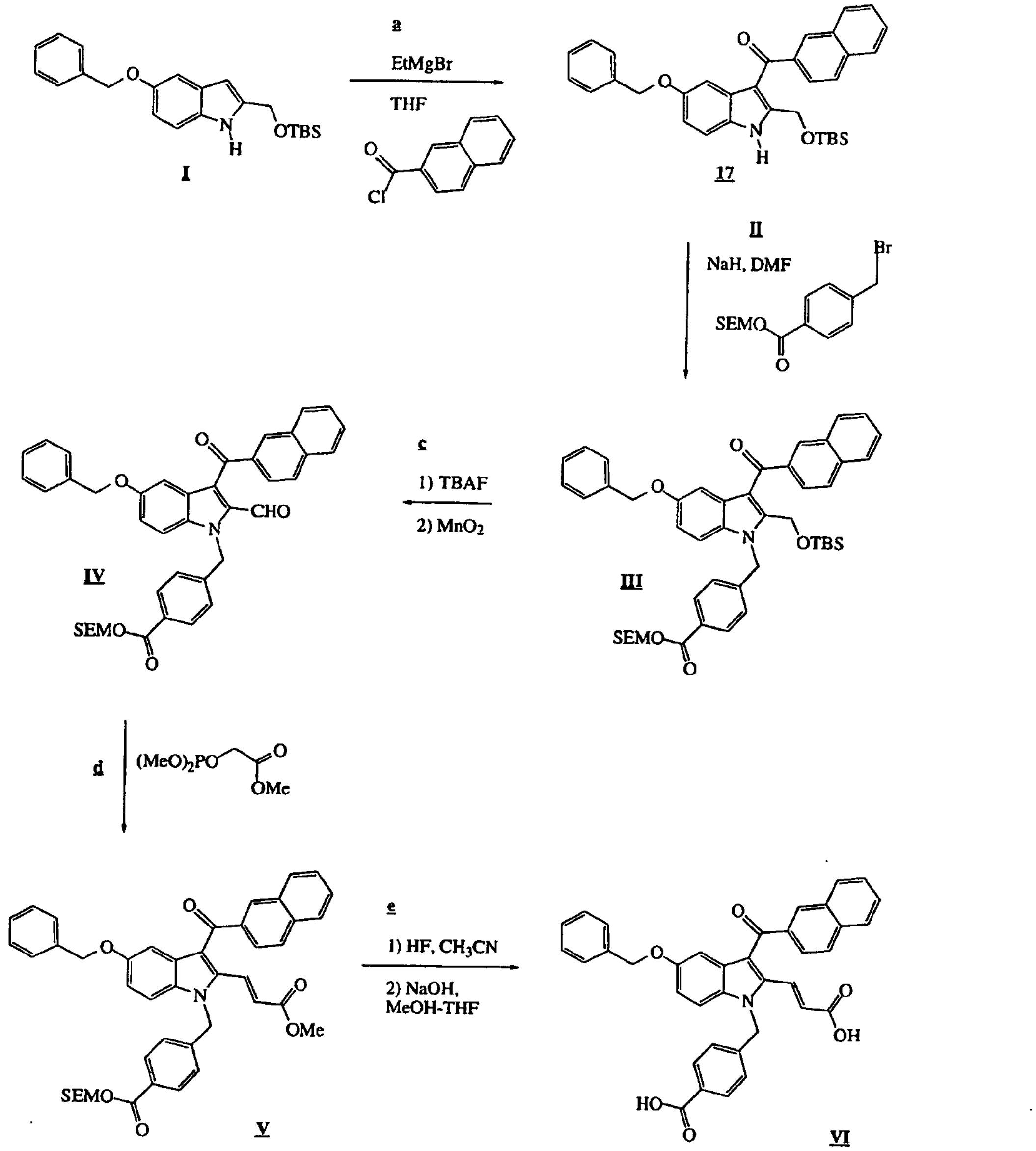
Method E

The starting indole, with or without C2 substitution, was functionalized at C3 by using DMF/POCl3 conditions or the magnesium salt of the indole was acylated with a variety of acid chlorides to form the ketones. These products where then N-alkylated by the action of a strong base and a variety of alkyl or aryl halo esters. When R' is a nitro group, at this time the nitro was reduced with Pt/C and H2 or copper acetate and sodium borohydride to the amine which was then acylated with a variety of acid chlorides, isocyantes, chloroformates, reductively alkylated with amines or coupled with acids. The resulting esters were hydrolyzed to the desired acids which could further be transformed to the acylsulfonamide.

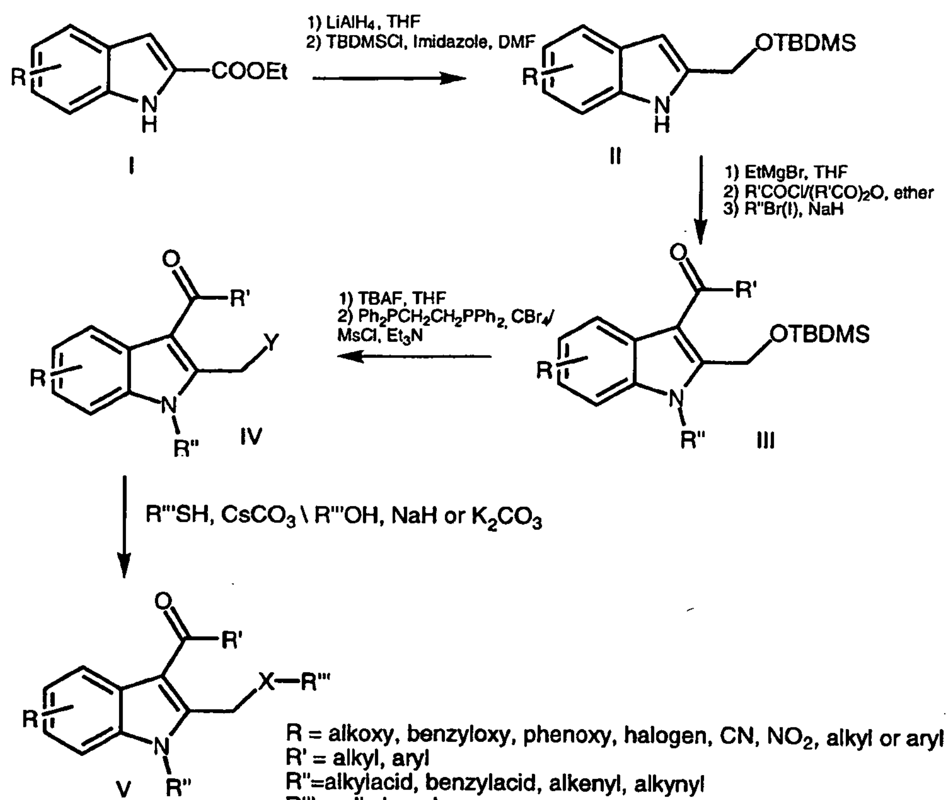
Method A


NCS
DMF
50 °C
1)NaOH
MeOH, THF
2)CDI/THF
3) NaBH4, EtOH
TBDMSCl
imidazole, DMF
NaH, DMF
Pt/C/H2
THF
C5H9COCl
CH2Cl2
Ph3PBr2
CH2Cl2
R1H
Cs2CO3
DMF
R1
Aryl thio ether
alkyl thio ether
aryl ether
alkyl ether

Method B

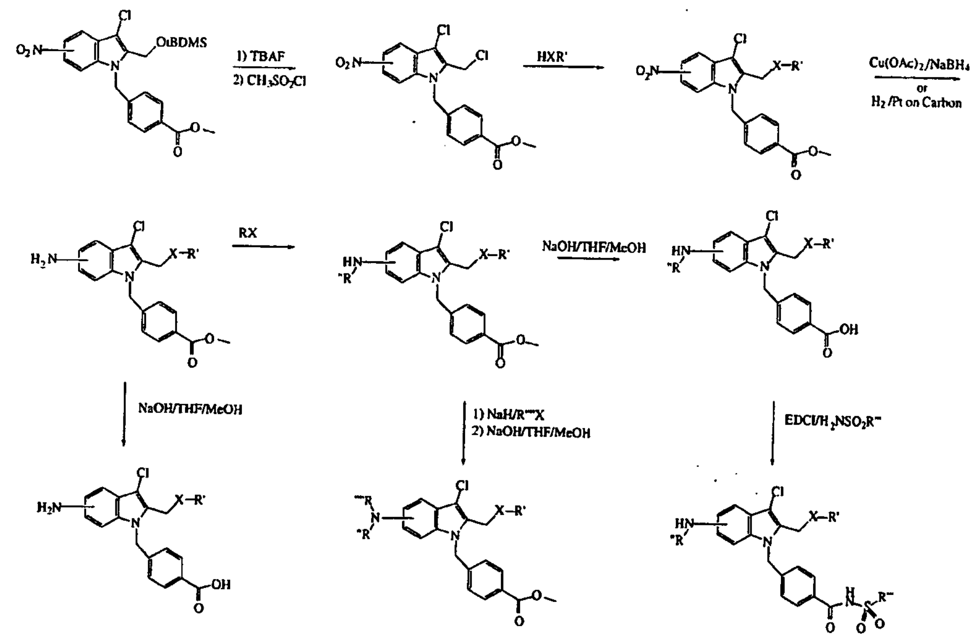

a
EtMgBr
THF
I
17
II
NaH, DMF
c
1) TBAF
2) MnO_2
IV
III
d
$(MeO)_2PO$
OMe
e
1) HF, CH_3CN
2) NaOH, MeOH-THF
V
VI

Method C

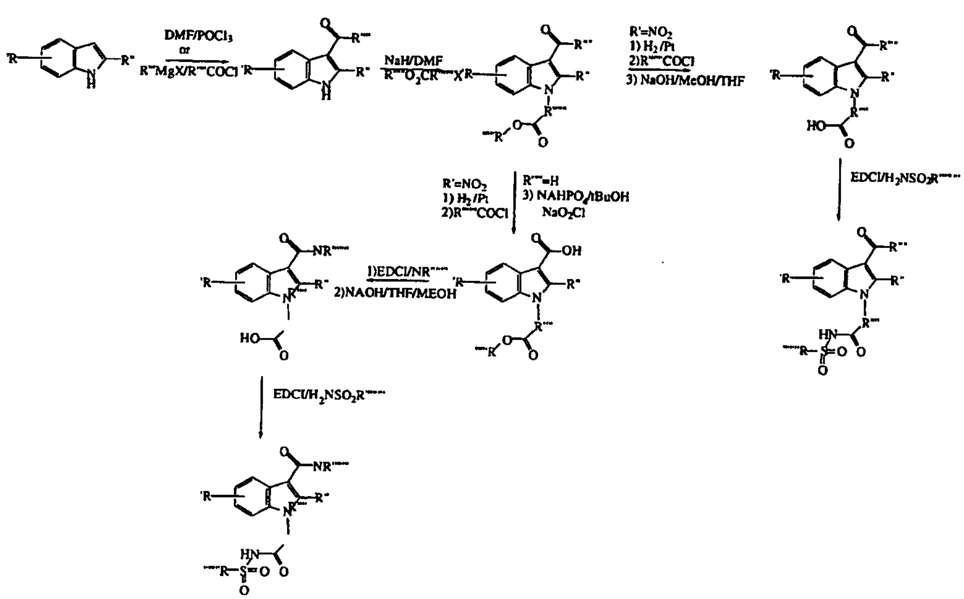


R = alkoxy, benzyloxy, phenoxy, halogen, CN, NO_2, alkyl or aryl
R' = alkyl, aryl
R"=alkylacid, benzylacid, alkenyl, alkynyl
R''' = alkyl, aryl
X = O,S
Y = halogen, mesylate

Method D



Method E



Example 1
4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(phenethylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step 1 - Ethyl 5-nitroindole-2-carboxylate (21.1 g) was dissolved in DMF (500 mL). To this dark brow solution, a solution of N-chlorosuccinamide was added (12 g in 125 mL DMF) over a period of 5 minutes. The reaction mixture was heated to 50 °C for 1.5 h. Reaction completion was determined by TLC. The reaction was cooled to room temperature, diluted with water (2 L), and extracted with ethyl acetate (3 X 1 L). The organic layers were combined , dried over $MgSO_4$, filtered and concentrated. The result was the desired ethyl ester (96 g wet with DMF) which was carried on to the next step without further purification.

Step 2 - The ethyl ester was dissolved in methanol (400 mL) and THF (800mL). To this clear, brown solution 2 N NaOH was added (450 mL). The black mixture was stirred at room temperature overnight. The reaction was not quite complete (TLC) therefore an additional 7.2 g of NaOH pellets were added. After 7 h the reaction was complete. Approximately 1 L of solvent was removed by rotary evaporation. The residue was dissolved with ethyl acetate and water and acidified with 2 N HCl to pH 2. The mixture was then extracted with ethyl acetate (3 X 1 L). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the acid (24.3 g, 100%) as a brown solid.

Step 3 - The carboxylic acid (24 g) was dissolved in THF (700 mL). CDI (16.2 g) was added to this clear, amber-colored solution. The mixture was stirred at room temperature for 1.5 h, during which time it became a light brown suspension. The reaction was cooled in an ice bath. Sodium borohydride (10.8 g) was added slowly. Ethanol was then added (140 mL). The evolution of gas was observed. After 2 h, TLC analysis indicated that the reaction was complete. To adjust the pH to 2, 2 N HCl was added. The reaction was then extracted with ethyl acetate (3 X 600 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to yield the desired alcohol (28.5 g) as a brown solid.

Step 4 - The alcohol prepared above (25.4 g), imidazole (18.6 g), and *tert*-butyldimethylsilyl chloride (13.3 g) were dissolved in DMF (350 mL). The reaction was stirred overnight and found not to be complete. Therefore imidazole (18.7 g) and t-butyldimethylsilyl chloride (18.6 g) were added. After 1 h, the reaction was complete. Water (1.5 L) was added and the mixture was extracted with ethyl acetate (3 X 500 mL). The combined organic layers were evaporated to dryness to give the crude 5-*tert*-

butyldimethylsilyl-protected alcohol. The crude material was dissolved in ethyl acetate, absorbed onto silica gel, and evaporated to dryness. After loading onto a silica gel column and eluting with 15% ethyl acetate in hexanes, the desired protected alcohol (18.5 g, 69% from step 1) was isolated as bright yellow crystals.

Step 5 - The *tert*-Butyldimethylsilyl-protected alcohol (1.0 g) was dissolved in DMF (10 mL). The yellow solution was cooled in an ice bath. Sodium hydride (147 mg) was added. After 15 minutes, 4-(bromomethyl)benzoate (807 mg) was added to the dark red solution. After 15 minutes, TLC analysis indicated that the reaction was complete. The reaction was poured into cold 1 N HCl. Water (800 mL) was added and the solution was extracted with ethyl acetate. The combined organic layers were evaporated to dryness to give the crude N-alkylated indole as an orange solid. The crude solid as absorbed onto silica gel, added to a silica gel column and eluted with 15% ethyl acetate in hexanes to give the desired N-alkylated indole (1.05 g, 73%) as a yellow solid.

Step 6 - N-alkylated indole (3.8 g) was dissolved in THF (50 mL) and 5% Pt/C (1.6 g) was added. Hydrogen was purged in and the reaction was stirred at room temperature overnight. The reaction was filtered (celite) and concentrated. Column chromatography (35% ethyl acetate in hexane) gave the desired amine (1.7 g) as an off-white solid.

Step 7 - To a solution of the above amine (1.6 g, 3.5 mmol) in CH_2Cl_2 (10 mL) and saturated sodium bicarbonate (10 mL) was added cyclopentyl carbonyl chloride (0.467 ml, 1.1 eq). The reaction was stirred 45 min, taken up in ethyl acetate (100 mL), washed with brine (3 X 20 mL), dried ($MgSO_4$), filtered and concentrated. Chromatography (20% ethyl acetate/hexanes) afforded the desired product (1.55 g, 82%) as a pale yellow oil.

Step 8 - To a solution of the above amide (0.6 g, 1.1 mmol) in dichloroethane (3 mL) at 0 °C is added dibromotriphenylphosphorane (0.5 g, 1.1 eq). The reaction is stirred to room temperature over 2h, taken up in ethyl acetate (50 mL), washed with brine (3 X 10 mL), dried ($MgSO_4$) and concentrated and carried immediately to the next step.

Step 9 - To a solution of the crude bromide prepared above (0.54 mmol) in DMF (2 mL, degassed) is added phenethyl mercaptan (0.08 g, 1.1 eq) followed by cesium carbonate (0.21 g, 1.2 eq). The reaction is stirred 1h, taken up in ethyl acetate (20 mL), washed with brine (3 X 5 mL), dried ($MgSO_4$), filtered and concentrated. Chromatography (25% ethyl acetate/hexanes) afforded the desired compound (0.17 g, 56%) as a colorless oil.

Step 10 - To a solution of the above ester in THF (1 mL) and MeOH (0.5 mL) is added NaOH (0.28 mL, 5 M, 5 eq). The reaction is stirred 4 h, acidified with sodium biphosphate, poured into ethyl acetate, washed with brine and dried ($MgSO_4$). The title compound (0.157, 98%) was triturated from ethyl acetate with hexanes.

Each of the compounds of the following Examples 2 through 11 was prepared by a first step as illustrated in Example 1, step 9, using the appropriate thiol, followed by a second step as described in Example 1, step 10.

Example 2

4-[(3-chloro-5-[(cyclopentylcarbonyl)amino]-2-{[(2-furylmethyl)sulfanyl]methyl}-1H-indol-1-yl)methyl]benzoic acid

Example 3

4-[(3-chloro-5-[(cyclopentylcarbonyl)amino]-2-{[(4-hydroxy-6-phenyl-2-pyrimidinyl)sulfanyl]methyl}-1H-indol-1-yl)methyl]benzoic acid

Example 4

4-{[3-chloro-5-[(cyclopentylcarbonyl)amino]-2-({[4-(2-thienyl)-2-pyrimidinyl]sulfanyl}methyl)-1H-indol-1-yl]methyl}benzoic acid

Example 5

4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(2,4-dibromophenoxy)methyl]-1H-indol-1-yl}methyl)benzoic acid

Example 6

4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(cyclopentylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Example 7

4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(propylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Example 8

4-({2-{[4-(tert-butyl)phenoxy]methyl}-3-chloro-5-[(cyclopentylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid

Example 9
4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(2-quinolinylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Example 10
4-[(3-chloro-5-[(cyclopentylcarbonyl)amino]-2-{[(cyclopropylmethyl)sulfanyl]methyl}-1H-indol-1-yl)methyl]benzoic acid

Example 11
4-({2-[(benzhydrylsulfanyl)methyl]-3-chloro-5-[(cyclopentylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid

The compounds of the following Examples 12 through 14 were prepared by:

Step 1 - The material prepared in Example 1, step 6, was acylated at the 5-amino position using the protocol of Example 1, step 7, with the appropriate acylating reagent.

Step 2 - The title compound was prepared from the intermediate of Step 1 following the procedure described in Example 1, steps 8 through 10, using the appropriate thiol.

Example 12
4-({5-[(3-carboxypropanoyl)amino]-3-chloro-2-[(phenethylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Example 13
4-[(5-[(3-carboxypropanoyl)amino]-3-chloro-2-{[(3-methylbenzyl)sulfanyl]methyl}-1H-indol-1-yl)methyl]benzoic acid

Example 14
4-({2-({[4-(tert-butyl)benzyl]sulfanyl}methyl)-5-[(3-carboxypropanoyl)amino]-3-chloro-1H-indol-1-yl}methyl)benzoic acid

Example 15

4-({3-chloro-5-(3-furoylamino)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

The title compound was prepared as described in Example 43 using the appropriate acylating reagent.

The following Examples 17 through 21 were prepared as described in Example 43 using the appropriate acylating reagent.

Example 17

4-({3-chloro-5-{[3-(diethylamino)propanoyl]amino}-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Example 18

4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(3-thienylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid

Example 19

4-({5-{[(benzylamino)carbonyl]amino}-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Example 20

4-({5-{[(butylamino)carbonyl]amino}-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Example 21

3-[({1-(4-carboxybenzyl)-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-5-yl}amino)carbonyl]benzoic acid

Example 22

4-{[5-(benzyloxy)-2-[(E)-2-carboxyethenyl]-3-(2-naphthoyl)-1H-indol-1-yl]methyl}benzoic acid

step 1

A solution of 2(tert -butyldimethylsilyloxymethyl)-5-benzyloxyindole (2.0g, 5,4mmol) in anhydrous ether (10ml) was cooled to -78^{0}C and a solution of ethylmagnesium bromide (3.0M in ether, 4.0ml, 12.0mmol) was added dropwise. The mixture was stirred at -60^{0}C to -65^{0}C for 2h during which time the homogeneous solution became a yellow slurry. A

solution of naphthoyl chloride (2.28g, 12.0mmol) in ether (8ml) was then added. After stirring for 2h at -60^{0}C to -40^{0}C the reaction was carefully quenched with saturated aqueous sodium bicarbonate and diluted with EtOAc. The combined organic layers were washed with brine, dried and concentrated. Flash chromatography (Hex/Acetone, 6/1) gave 2.2g (78%) of 17 as a yellow foam.

step 2

To an ice-cold (0C) solution of the intermediate above (1.0g, 1.9mmol) in DMF (10ml) was added sodium hydride (0.12g, 2.1mmol). The ice bath was removed after 10 min and the reaction was stirred at rt for 30min at which time the bromomethyl SEM ether (0.5ml, 2,8mmol) was added dropwise. The mixture was stirred at rt for 4h, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated. Flash chromatography (Hex/Acetone, 6/1) afforded 1.22g (81%) of the desired intermediate as an off-white foam.

step 3

To a solution of the above (6.6g, 8.4mmol) in THF (80ml) was added tetrabutylammonium fluoride (1.0M in THF, 21ml). The reaction was stirred at rt for 2h, water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water, brine, dried and concentrated. Flash chromatography (Hex/EtOAc, 4:1) gave 3.8g (67%) of the alcohol as a thick colorless oil. The alcohol was dissolved in THF (50ml) and MnO_2 (5.5g, 63.2mmol) was added. The reaction was stirred for 22h and filtered through a pad of Celite. Concentration of the filtrate gave 3.7g (96%) of the desired intermediate as a light yellow foam.

step 4

To an ice-cold (0^{0}C) solution of trimethylphosphonoacetate (0.12ml, 0.7mmol) in DMF (5ml) was added sodium hydride (0.027g, 0.8mmol). After 30min a solution of the above intermediate (0.5g, 0.7mmol) in 5ml of DMF was added. The ice bath was removed and the reaction was allowed to stir overnight. Water was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Flash chromatography (Hex/EtOAc, 3/2) gave 0.2g of the desired intermediate (37%) as a white foam.

step 5

4-{[5-(benzyloxy)-2-[(E)-2-carboxyethenyl]-3-(2-naphthoyl)-1H-indol-1-yl]methyl}benzoic acid

To a solution of the intermediate above (0.5g, 0.7mmol) in acetonitrile (10ml) was added aqueous 48% hydrofluoric acid (5ml). After 2h, water was added and the product was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over magnesium sulfate. Concentration gave a crude solid that was dissolved in THF (2ml) and MeOH (1ml) and 1N sodium hydroxide solution (2ml). After stirring overnight at rt the reaction was acidified to pH=3 with 10% HCl solution and extracted with ethyl acetate. Flash chromatography (CH2Cl2/MeOH, 10/1) gave the title compound (0.2g, 50%) as a white solid.

Example 23

4-({3-acetyl-5-(benzyloxy)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step 1: Ethyl 5-benzyloxy-2-indolcarboxylate (30 g, 102 mmol) is dissolved in 250 mL of THF and cooled to 0° C and Lithium Aluminum Hydride (LAH) (255 mL of a 1.0 M solution in THF) is added via addition funnel over 40 minutes. The reaction was stirred a further 2 hours at 0° C and then worked up by the addition of 4N NaOH (190 mL). The resulting salts are filtered and washed with ethyl acetate (3X400 mL), the filtrates are combined and dried over $MgSO_4$ and concentrated to yield 24.8 g.

Step 2: The crude indole alcohol prepared in step 1 (8.3 g, 32.6 mmol) is dissolved in DMF (10.5 mL). To this solution is added imidazole (5.5g, 81.5 mmol) and t-butyldimethylsilyl chloride (5.4g, 35.8 mmol). The mixture is stirred at room temperature overnight. The reaction is poured into water and extracted with ethyl acetate (3X). Organic layers are dried over magnesium sulfate and concentrated. The crude material is purified on a silica gel column using 19:1 Hexane:Ethyl acetate to give pure product (11.9g, 31 mmol, 94 % yield, TLC _ 0.8 Rf in Toluene:Ethyl acetate 2:1)

Step 3: A solution of the silyl protected indole prepared in step 2 (2 g, 6.56 mmol) in ether (20 mL) was added dropwise to ethyl magnesium bromide (2.4 mL of a 3M solution in ether, 7.2 mmol) in ether (10 ml), the latter maintained at -78°C. The reaction was stirred at -60°C for 2 hr. Next acetylchloride (0.51 mL, 7.2 mmol) in ether (4 mL) was added slowly. The reaction maintained between -50°C and -60°C for another 2 hrs. The reaction was then quenched with saturated sodium bicarbonate. Extracted with ethyl acetate (3X). Organic layers were dried over magnesium sulfate and concentrated. The

crude material was purified on a silica gel column using 19:1 Hexane:Ethyl acetate to give pure product (1.2 g, 50%).

Step 4: To the indole (1.2 g, 2.9 mmol, prepared in step 3 above) in 10.5 ml of DMF, sodium hydride (0.13g, 60% oil dispersion, 3.23 mmol) is added at room temperature. The reaction is stirred for 30 minutes. Methyl (4-bromomethyl) benzoate (0.81 g, 3.53 mmol) is added at this time and the reaction stirred overnight. On completion of the reaction (monitored by TLC) it is quenched with water, extracted with ethyl acetate (3X). Organic layers are dried over magnesium sulfate, concentrated and used for the next step.

Step 5: A mixture of silyl protected indole prepared in step 4 above (0.65 g, 1.2 mmol) and tetra-butyl ammoniumfluoride (2.9 mL of a 1M solution in tetrahydrofuran, 2.9 mmol) in tetrahydrofuran (6 mL) were stirred at room temperature for one hour. At this time the reaction was diluted with ethyl acetate and water, extracted with ethyl acetate (3X), dried over magnesium sulfate and concentrated. The crude material was purified on silica gel using 1:1 Hexane:Ethyl acetate to yield pure alcohol (0.47 g, 91 %).

Step 6: The indole alcohol (0.3 g, 0.68 mmol), carbon tetrabromide (0.27 g, 0.81 mmol) and 1,3-bis(diphenylphosphino)propane (0.21 g, 0.51 mmol) were taken up in dichloromethane (8.4 mL) and stirred for 16 hours at which time the reaction was diluted with dichloromethane and half saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate (3X) dried over magnesium sulfate and concentrated. The crude material was purified on silica gel using2:1 Hexane:Ethyl acetate to yield pure alcohol (0.27 g, 78 %).

Step 7: The indole bromide prepared in step 6 (0.1 g, 0.2 mmol) was dissolved in dimethylformamide (0.4 mL, degassing the solvent is strongly recommended) cesium carbonate (0.2 g, 0.6 mmol) was added and then ethyl 2 naphthalenethiol (0.034g, 0.22 mmol) was added and the mixture was stirred for 1 day, then the reaction was poured into 1/2 saturated ammonium chloride and extracted with ethyl acetate (3X), dried, concentrated and chromatographed (Hexane:Ethyl acetate 3:1) to yield 0.05 g (57%) of pure product.

Step 8: The ester (0.2 g, 0.34 mmol) prepared in step 7 above is dissolved in 4.0 mL of 1/1 THF/ methanol and then 1N sodium hydroxide (2.5 mL) is added and the resulting mixture is stirred for 16 hours at RT, workup gave crude product that is purified via

chromatography (1:1 Hexane:Ethyl acetate with 1% acetic acid) to yield (0.17 g, 85%) of solid.

Example 24

4-{[5-(benzyloxy)-2-[(2-naphthylsulfanyl)methyl]-3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl]methyl}benzoic acid

Step 1: This intermediate was prepared from the indole, prepared in step 2 of Example 23 and trifluoroacetic anhydride, according to the procedure described in step 3 of Example 23.

Step 2: This intermediate was prepared according to the procedure described in step 4 of Example 23, but using the indole derivative prepared in step 1 above and methyl (4-bromomethyl) benzoate.

Step 3: To a solution of the indole alcohol prepared in step 2 (0.1 g, 0.2 mmol) and triethylamine (0.04 mL, 0.3 mmol) in dichloromethane (0.4 mL), methanesulphonyl chloride (0.02 mL, 0.24 mmol) is added dropwise at 0°C. The reaction is stirred for 1.5h and then the dichloromethane removed. To the residue in 0.4 mL of DMF at 0°C 2-naphthalene thiol (0.034 g, 0.22 mmol) is added. Next $CsCO_3$ (0.96 g, 0.3 mmol) is added and the reaction mixture stirred at room temperature overnight, then the reaction was poured into brine and extracted with ethyl acetate (3X), dried, concentrated and chromatographed (Hexane:Ethyl acetate 3:1) to yield 0.064 g (50%) of pure product.

Step 4: The title compound was prepared from ester, prepared in step 3 above, according to the procedure described in step 8 of Example 23.

Example 25

4-({5-[(4-aminobutanoyl)amino]-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

step 1: The t-butylsilyl protected alcohol (25g) from step 6 of Example 1, was dissolved in THF(200mL) and then tetrabutylammonium flouride (125mL of a 1.0 M solution) was added and the mixture was stirred for 10 minutes at room temperature and then the reaction was diluted with water and the THF was concentrated, ethyl acetate was added and the layers were separated, the aqueous layer was extracted three times with ethyl acetate, the combined organic layers were dried and concentrated to yield the desired alcohol (21.5 g).

Step2: The alcohol (13.1g) from step 1 was suspended in dichloromethane (450 mL), cooled to 0°C and triethylamine(10 mL) and methanesulfonyl chloride (4.0 mL) were added and the resulting mixture was left to warm to room temperature overnight at which time it was diluted with saturated sodium bicarbonate was added and the reaction was diluted with dichloromethane, the layers were separated, the aqueous layer was extracted three times with dichloromethane, the combined organic layers were dried, concentrated to yield the desired chloride (13.5g).

Step 3: To the chloride (13.5g) generated in step 2 was added DMF (150 mL), cesium carbonate (33.5 g) and then the solution was degassed by bubbling argon through the solution for 20 minutes and then 2-naphthalene thiol was added and the reaction was stirred for 20 minutes at room temperature, then water was added as was ethyl acetate, the layers were separated and the combined organic layers were concentrated to a slurry which was stirred overnight and then the slurry was filtered and the solid was triturated with 40% ethyl acetate in hexane to deliver the desired disulfide (12.2 g) in 69% yield.

Step 4: The product from step three (11.25 g) was dissolved in THF (500 mL), methanol (500mL) and then copper II acetate (19.2 g) suspended in water (300 mL) was added as was more THF (100mL) and then sodium borohydride (11.2 g) was added portionwise. After 2.5 hours of stirring at room temperature the foamy black solution was diluted with saturated sodium bicarbonate and the layers were separated, the aqueous layer was extracted three times with ethyl acetate, the combined organic layers were dried and concentrated and chromatographed to yield the desired amine (9.0 g) in 85% yield.

step 5: The amine from step 4 above was coupled to fmoc protected 4-aminobutyric acid following the procedure outlined in step 1, Example 43, followed by trituration with dichloromethane delivered the amide in 43% yield.

Step 6 : The amide (1.0 eq) from step 5 was dissolved in methanol (5 mg/ml) and piperidine (0.024 ml/mg) and then the reaction was stirred at room temperature for two hours, concentrated and chromatographed to yield the desired product in quantitative yield.

Step 7: The amino ester from step 6 was hydrolyzed using the conditions outlined for step 2 of Example 43 to deliver the title compound in 54%.

Example 26

4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

step1: The amine (1.0 eq) from step 4 of Example 25 was dissolved in CH_2Cl_2 (0.3M) and then an equivalent amount of saturated sodium bicarbonate was added and then the appropriate acid chloride (1.2 eq) was added. The biphasic reaction mixture was vigorously stirred until TLC analysis indicated that the reaction was complete (generally a few hours) and then the reaction was diluted with dichloromethane and water, the layers were separated, the aqueous layer was extracted three times with dichloromethane, the combined organic layers were dried, concentrated and chromatographed, or used crude, to yield the desired amide in 50% yield.

Step 2: The ester from the previous step was dissolved in THF/MeOH (3:1) and then 1N NaOH (3.0eq) was added and the reaction was stirred for until TLC analysis showed that the reaction was complete. The reaction was then concentrated, diluted with water, acidified to pH 2 with conc HCL, extracted with ethyl acetate 3X, the combined organics were dried over magnesium sulfate concentrated and purified via chromatography to yield the desired acid in 69% yield.

Example 27

4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(2-quinoxalinylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid

Step1: The amine from step 4 of Example 25 was treated with the appropriate acid chloride according to the general procedure for Example 71, step 1, to deliver the amide in 76% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 53% yield.

Example 28

4-({3-chloro-5-[(2,2-dimethylpropanoyl)amino]-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step1: The amine from step 4 of Example 25 was treated with the appropriate acid chloride according to the general procedure for Example 71, step 1, to deliver the amide in 100% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 79% yield.

Example 29

4-({5-{[(benzyloxy)carbonyl]amino}-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

step1: The amine from step 4 of Example 25 was treated with the appropriate acid chloride according to the general procedure for Example 71, step 1, to deliver the amide in 96% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid.

Example 30

4-({3-chloro-5-{[(cyclopentyloxy)carbonyl]amino}-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step1: The amine from step 4 of Example 25 was treated with acetic anhydride according to the general procedure for Example 71, step 1, to deliver the amide in 92% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid.

Example 31

4-({5-(acetylamino)-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step1: The amine from step 4 of Example 25 was treated with acetic anhydride according to the general procedure for Example 71, step 1, to deliver the amide in 77% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 29%.

Example 32

4-({5-{[(butylamino)carbonyl]amino}-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step1: THF (0.12M) was added to the amine (1.0 eq) generated in step 4, the reaction mixture was cooled to 0°C and then butylisocyanate (1.1 eq) was added and the mixture was warmed to room temperature overnight and the reaction was diluted with 1/2 saturated

ammonium chloride, the layers were separated, the aqueous layer was extracted three times with ethyl acetate, the combined organic layers were dried and concentrated and purified via chromatography to yield the desired urea in 57% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 41%.

Example 33
4-({5-{[(butylamino)carbonyl]amino}-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step 1: According to the procedure for Example 32, step 1, the amine was treated with benzyl isocyanate to deliver the title compound in 16% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 100%.

Example 34
4-({3-chloro-5-[(morpholinocarbonyl)amino]-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step 1: The amine (1.0 eq) generated above in step 4 was weighed into a flask along with 4-dimethyaminopyridine (1.5eq) and then they were taken up in dichloroethane (0.08 M) and then 4-morpholinecarbonyl chloride (1.5eq) was added and the reaction was stirred overnight at room temperature and then heated to 40°C for 4 hours and then worked up by the addition of ethyl acetate and 1/2 saturated ammonium chloride, the layers were separated, the aqueous layer was extracted three times with ethyl acetate, the combined organic layers were dried and concentrated and purified via chromatography to yield the desired urea in 100% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 79%.

Example 35
4-({5-(benzylamino)-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step 1: The amine (1.0eq) from step 1 was dissolved in dichloroethane and then benzaldehyde (1.0 eq) was added followed by acetic acid (1.0 mL/1mmol) and the reaction was stirred for 20 minutes and then the sodium triacetoxyborohydride (1.3 eq)

was added and the reaction was stirred overnight at room temperature, quenched by the addition of aqueous diethanolamine and dichloromethane the layers were separated, the aqueous layer was extracted three times with dichloromethane , the combined organic layers were dried and concentrated and purified via chromatography to yield the desired urea in 74% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 49%.

Example 36

4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(3-phenoxybenzyl)amino]-1H-indol-1-yl}methyl)benzoic acid

Step 1: According to the procedure for step 1 of Example 35 the amine from step 4 of Example 25 was treated with the appropriate aldehyde to yield the desired secondary amine in 38% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 87%.

Example 37

4-({3-chloro-5-[(cyclopentylcarbonyl)(methyl)amino]-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step 1: To the ester generated in step 1 of the synthesis of Example 27 was added DMF (0.05M), the reaction was cooled to 0°C and then sodium hydride (10 eq) was added and the mixture was stirred for 30 minutes, methyl iodide (10eq) was then added and the resulting mixture was stirred overnight at room temperature and then diluted with ethyl acetate and 1/2 saturated ammonium chloride, the layers were separated, the aqueous layer was extracted three times with ethyl acetate, the combined organic layers were dried and concentrated and purified via chromatography to yield the desired methylated amide in 56% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 57%.

Example 38

4-({5-[acetyl(benzyl)amino]-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step1: The amide synthesized in step 1 of Example 31 was benzylated according to the procedure in step 1 for Example 37 to yield the tertiary amide in 90% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 41%.

Example 39

4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(tetrahydro-3-furanylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid

Step 1: To the indole amine (1.0 eq) was added the acid (1.2 eq) the dimethylaminopyridine (10 mol %), 1-(3dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 eq) and then DMF(0.3M) and the reaction was stirred under nitrogen for 24 hours at room temperature at which time it was poured into 1/2 saturated ammonium chloride solution and ethyl acetate and then the layers were separated and the aqueous layer was extracted 3 times, the combined organic layers were washed with water 2X, dried, concentrated and chromatographed to yield 55% of the title compound.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 55%.

Example 40

4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(3-thienylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid

step 1: According to the procedure for step 1 of Example 39 the amine from step 4 of Example 25 was treated with the requisite acid to yield the amide in 100% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 21%.

Example 41

4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(1-adamantylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid

Step 1: According to the procedure for step 1 of Example 39 the amine from step 4 of Example 25 was treated with the requisite acid to yield the amide in 100% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 35%.

Example 42

3-[({1-(4-carboxybenzyl)-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-5-yl}amino)carbonyl]benzoic acid

Step 1: According to the procedure for step 1 of Example 39 the amine from step 4 of Example 25 was treated with the requisite acid to yield the amide in 100% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 20%.

Example 43

4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(3-phenylpropanoyl)amino]-1H-indol-1-yl}methyl)benzoic acid

Step 1: According to the procedure for step 1 of Example 39 the amine from step 4 of Example 25 was treated with the requisite acid to yield the amide in 100% yield.

Step 2: The ester from step 1 was hydrolyzed under the conditions outlined for step 2 of Example 26 to yield the desired acid in 32%.

Example 44

4-({5-amino-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

step 1: The amine generated in step 4 was hydrolyzed according to the procedure for step 2 of Example 26 to yield 79% yield.

Example 45

N-{3-chloro-1-(4-{[(methylsulfonyl)amino]carbonyl}benzyl)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-5-yl}cyclopentanecarboxamide

Step 1: To Example 26 (1.0 eq), EDCI (1.5 eq), DMAP (1.0 eq), methane sulfonamide (1.0 eq) in a flask under nitrogen was added DMF (0.08M) and the reaction was stirred overnight at room temperature and then worked up by the addition of 1/2 saturated ammonium chloride solution and ethyl acetate and then the layers were separated and the aqueous layer was extracted 3 times, the combined organic layers were washed with water 2X, dried, concentrated and chromatographed to yield 27% of the title compound.

Example 46

N-{3-chloro-2-[(2-naphthylsulfanyl)methyl]-1-[4-({[(4-nitrophenyl)sulfonyl] amino}carbonyl)benzyl]-1H-indol-5-yl}cyclopentanecarboxamide

Step 1: To Example 26 was added the appropriate sulfonamide under the conditions outlined for step 1, Example 45, to yield the desired acylsulfonamide in 43% yield.

Example 47

N-{3-chloro-1-[4-({[(2-methylphenyl)sulfonyl]amino}carbonyl)benzyl]-2-[(2-naphthylsulfanyl)methyl]-1H-indol-5-yl}cyclopentanecarboxamide

Step 1: To Example 26 was added the appropriate sulfonamide under the conditions outlined for step 1, Example 45, to yield the desired acylsulfonamide in 40% yield.

Example 48

N-[3-chloro-2-[(2-naphthylsulfanyl)methyl]-1-(4-{[(phenylsulfonyl)amino] carbonyl}benzyl)-1H-indol-5-yl]cyclopentanecarboxamide

Step 1: To Example 26 was added the appropriate sulfonamide under the conditions outlined for step 1, Example 45, to yield the desired acylsulfonamide in 40% yield.

Example 49

N-{3-chloro-2-[(2-naphthylsulfanyl)methyl]-1-[4-({[(trifluoromethyl)sulfonyl] amino}carbonyl)benzyl]-1H-indol-5-yl}cyclopentanecarboxamide

Step 1: To Example 26 was added the appropriate sulfonamide under the conditions outlined for step 1, Example 45, to yield the desired acylsulfonamide in 67% yield.

Example 50

4-[5-[(cyclopentylcarbonyl)amino]-2-[(2-naphthyloxy)methyl]-3-(1-pyrrolidinylcarbonyl)-1H-indol-1-yl]butanoic acid

Step 1

The Ethyl 5-nitroindole-2-carboxylate (1 eq) was dissolved in THF/MeOH/H_2O (3:1:1 0.21 M) followed by addition of $LiOH{\cdot}H_2O$ (1.38 eq), stirred at 25°C, overnight. Reaction mixture was then acidified to pH=1 with 1N HCl solution and extracted with ethyl acetate. Workup with water, brine, drying and concentration afforded the crude product in 99% yield.

Step 2

The crude acid (1 eq) from step 1 was dissolved in THF (0.14 M) and to this was added carbonyl diimidazole (1 eq), stirred at 25°C for 1.5h. Reaction mixture was then cooled to 0°C. Sodium borohydride (2.86 eq) was added in several portions followed by the addition of EtOH (0.71 M), stirred at 25°C, overnight. Reaction mixture at this point was acidified with 2N HCl to pH=2 and extracted with ethyl acetate. Workup with water, brine, drying and concentration afforded the crude product in 95% yield.

Step 3

In an oven dried flask was added the crude indole alcohol (1 eq) from step 2 followed by anhydrous DMF (0.135 M). To this was then added imidazole (1.3 eq) and TBSCl (1.2 eq), stirred at 25°C for 1 h. Workup with ethyl acetate/water followed by chromatographic purification afforded the desired product in 70% yield.

Step 4

The silyl protected indole (1 eq) from step 3 was dissolved in anhydrous DMF (0.13 M) in an oven dried flask. To this was added NaH (60% dispersion in mineral oil, 1.2 eq) and stirred at 25°C for 1 h after which ethyl 4-bromobutyrate (1.2 eq) and KI (1.2 eq) were added. Reaction mixture was then heated at 60°C for 2 h. Workup with ethyl acetate/water followed by chromatographic purification afforded the desired product in 93% yield.

Step 5

Dissolved the alkylated indole (1 eq) from step 4 in THF (0.05 M) and to this was added TBAF (1.0 M/THF, 1.1eq) dropwise at 25°C, stirred for 1 h. Workup with ethyl acetate/water followed by chromatographic purification afforded the desired product quantitatively.

Step 6

Dissolved the indole alcohol (1 eq) from step 5 in anhydrous DMF (0.16 M) followed by the addition of $POCl_3$ (10 eq) dropwise at 0°C. Heated at 80°C, overnight. Workup with ethyl acetate/water and washing the organic layer with 1N NaOH, water, brine followed by concentration and chromatographic purification afforded the desired product in 64% yield.

Step 7

A mixture of the chloro aldehyde derivative (1 eq) from step 6, 325 mesh K_2CO_3 (2.4 eq), 2-naphthol (1.2 eq) and KI (1.2 eq) was suspended in anhydrous acetonitrile (0.2 M) and heated at 70°C for 1.5 h. Workup with ethyl acetate/water followed by chromatographic purification afforded the desired product in 65% yield.

Step 8

Dissolved the naphthyloxy indole derivative (1 eq) from step 7 in anhydrous THF (0.023 M) and to this was added 5% Pt/C (40wt%) under nitrogen and hydrogenated with a H_2 balloon for 2.5 h. Reaction mixture was then filtered through Celite and concentrated to afford the crude product in 96% yield.

Step 9

The amino indole derivative (1 eq) from step 8 was dissolved in anhydrous CH_2Cl_2 (0.07 M) followed by dropwise addition of Et_3N (1.4 eq) and cyclopentanecarbonyl chloride (1.2 eq) at 0°C. Stirred at 25°C for 0.5 h after which the reaction mixture was quenched with saturated $NaHCO_3$ solution and stirred overnight. Organic layer was separated and washed with brine, dried. Product was obtained in 66% yield after recrystallization from 30% ethyl acetate/hexane.

Step 10

The indole from step 9 (1 eq) was weighed into a flask along with NaH_2PO_4 (12 eq), t-butyl alcohol (0.13 M), water (0.13 M), 2-methyl-2-butene (46 eq) and to this mixture was added NaO_2Cl (12 eq) at 25°C. Reaction mixture was then heated at 65°C, overnight. Workup with ethyl acetate/water followed by trituration with CH_2Cl_2/hexane (4:6) at 0°C for 1 h afforded the desired product in 63% yield.

Step 11

The acid (1 eq) from step 10 was weighed into a flask and to this was added EDCI (3 eq), DMAP (1.2 eq), pyrrolidine (1.2 eq) followed by anhydrous THF (0.018 M) and the reaction mixture was then refluxed for 18 h. Worked up with ethyl acetate/water followed by washing the organic layer with 1N HCl, saturated bicarbonate and brine. Recrystallization from ethyl acetate/hexane (3:7) afforded the desired product in 89% yield.

Step 12

Dissolved the amide (1 eq) from step 11 in THF/MeOH/water (3:1:1, 0.025 M) and to this was added $LiOH \cdot H_2O$ (1.2 eq), stirred at 25°C, overnight. Workup with ethyl acetate/water followed by recrystallization from CH_2Cl_2/hexane (1:1) afforded the desired product in 98% yield.

Example 51

4-{5-[(cyclopentylcarbonyl)amino]-3-(morpholinocarbonyl)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoic acid

Step 1

Following step 11 of Example 50 and using morpholine yielded 87% of the desired product after recrystallization.

Step 2

Following step 12 above (Example 50) and using the corresponding morpholino amide afforded the desired product in 96% yield after recrystallization.

Example 52

N-[2-[(2-naphthyloxy)methyl]-1-(4-oxo-4-{[(trifluoromethyl)sulfonyl]amino}butyl)-3-(1-pyrrolidinylcarbonyl)-1H-indol-5-yl]cyclopentanecarboxamide

The acid Example 50 (1 eq) was weighed into a flask and to this was added EDCI (3 eq), DMAP (1.2 eq), trifluoromethanesulfonamide (1.2 eq) followed by anhydrous THF (0.04 M) and the reaction mixture was stirred at 25°C, overnight. Worked up with ethyl acetate/water followed by washing the organic layer with 1N HCl, saturated bicarbonate and brine. Trituration of crude product with CH_2Cl_2/hexane (1:2) at 0°C for 1 h afforded the desired product in 96% yield.

Example 53

N-[3-(morpholinocarbonyl)-2-[(2-naphthyloxy)methyl]-1-(4-oxo-4-{[(trifluoro-methyl)sulfonyl]amino}butyl)-1H-indol-5-yl]cyclopentanecarboxamide

Following step 1 above (Example 52) and using the corresponding acid Example 51 (step 4, scheme-4) afforded the desired product in 96% yield.

Example 53A

4-{5-[(cyclopentylcarbonyl)amino]-3-formyl-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoic acid

Step 1

Dissolved the indole (1 eq) from step 9 Example 50 in THF/MeOH/H_2O (3:1:1, 0.025 M) and to this was added LiOH.H_2O (1.2 eq), stirred at 25°C, for 4 h. Workup with ethyl acetate/1N HCl followed by trituration with CH_2Cl_2/hexane afforded the desired product in 74% yield.

Example 53 B

N-[3-formyl-2-[(2-naphthyloxy)methyl]-1-(4-oxo-4-{[(trifluoromethyl)sulfonyl]amino}butyl)-1H-indol-5-yl]cyclopentanecarboxamide

Step 1

The acid (1 eq) from step 1 of **Example 53A** was weighed into a flask and to this was added EDCI (1.35 eq), DMAP (1.1 eq), trifluoromethanesulfonamide (1.05 eq) followed by anhydrous THF (0.026 M) and the reaction mixture was stirred at 25°C, 3 h. Worked up with ethyl acetate/water followed by washing the organic layer with 0.05N HCl, saturated bicarbonate and brine. Chromatographic purification then afforded the desired product in 94% yield.

Example 54

5-[(cyclopentylcarbonyl)amino]-2-[(2-naphthyloxy)methyl]-1-(4-oxo-4-{[(trifluoromethyl)sulfonyl]amino}butyl)-1H-indole-3-carboxylic acid

Step 1

The product of **Step 1, Example 53B** (1 eq) was weighed into a flask along with NaH_2PO_4 (12 eq), t-butyl alcohol (0.12 M), water (0.12 M), 2-methyl-2-butene (50 eq) and to this mixture was added NaO_2Cl (11.8 eq) at 25°C. Reaction mixture was then heated at 60°C, 3 h and left overnight at 25°C. Workup with ethyl acetate/water followed by chromatographic purification and triturations with CH_2Cl_2/hexane (1:1) afforded the desired product in 57% yield.

Example 55

3-({4-[5-[(cyclopentylcarbonyl)amino]-2-[(2-naphthyloxy)methyl]-3-(1-pyrrolidinylcarbonyl)-1H-indol-1-yl]butanoyl}amino)benzoic acid

Step 1

The compound of Example 50 (1 eq) was weighed into a flask and to this was added EDCI (3 eq), DMAP (1.2eq), methyl 3-aminobenzoate (1.2 eq) followed by anhydrous THF (0.04M) and the reaction mixture was then stirred at 25°C for 2 d. Worked up with ethyl acetate/water followed by washing the organic layer with 1N HCl, saturated bicarbonate and brine. Recrystallization from ethyl acetate/hexane afforded the desired product in 88% yield.

Step 2

Dissolved the ester (1 eq) from step 1 in THF/MeOH/water (3:1:1, 0.024 M) and to this was added $LiOH \cdot H_2O$ (1.2 eq), stirred at 25°C, overnight at this point 1.2 eq of $LiOH \cdot H_2O$ was added and stirred for 2 h. Workup with ethyl acetate/1N HCl followed by trituration with CH_2Cl_2/hexane (1:1) at 0°C for 1h afforded the desired product in 92% yield.

Example 56

3-[(4-{5-[(cyclopentylcarbonyl)amino]-3-(morpholinocarbonyl)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]benzoic acid

Step 1

Following step 1 of Example 55 and using the product of Example 51 (see scheme-4 for synthesis) afforded the desired product in 85% yield after chromatographic purification.

Step 2

Following step 2 of Example 55 and using the corresponding morpholino from step 1 afforded the desired product in 91% yield.

Example 57

N-[2-[(2-naphthyloxy)methyl]-1-{4-oxo-4-[3-({[(trifluoromethyl)sulfonyl]amino}carbonyl)anilino]butyl}-3-(1-pyrrolidinylcarbonyl)-1H-indol-5-yl]cyclopentanecarboxamide

Step 1

The compound of Example 55 (1 eq) was weighed into a flask and to this was added EDCI (3 eq), DMAP (1.2 eq), trifluoromethanesulfonamide (1.2 eq) followed by anhydrous THF (0.04 M) and the reaction mixture was then stirred at 25°C, overnight. Worked up with ethyl acetate/water followed by washing the organic layer with 1N HCl,

saturated bicarbonate and brine. Trituration with CH_2Cl_2/hexane (8:2) afforded the desired product in 84% yield.

Example 58

N-(3-(morpholinocarbonyl)-2-[(2-naphthyloxy)methyl]-1-{4-oxo-4-[3-({[(trifluoromethyl)sulfonyl]amino}carbonyl)anilino]butyl}-1H-indol-5-yl)cyclopentanecarboxamide

Following step 1 of Example 57 and using Example 56 afforded the desired product in 84% yield.

Example 59

2-(4-{[5-(benzyloxy)-3-(1-naphthoyl)-1H-indol-1-yl]methyl}phenyl)acetic acid

Step 1: A solution of MeMgBr in butyl ether (1 M, 1.2 eq) was ice cooled. 4-Benzyloxy indole (1 eq) in CH_2Cl_2 (0.5 M) was added and the reaction mixture was allowed to warm to 25 °C. After the addition of 1-naphthoyl chloride (1 eq) in CH_2Cl_2 (1 M) the reaction was heated to reflux for 3 h. Quenching with aqueous NH_4Cl and extraction with $CHCl_3$ provided crude ketone, which was purified by recrystallization from hexane/$CHCl_3$/MeOH (53 % yield).

Step 2: An ice cooled solution of the ketone (1 eq) from step 1in DMF (0.2 M) was treated with NaH (60 % in mineral oil, 2.5 eq). 4-bromophenyl acetic acid (1.1 eq) in DMF (0.4 M) was added after 15 minutes and the resulting mixture was stirred overnight at 25°C. The reaction was quenched with 1N HCl and extracted with EtOAc. The organic extracts were dried and concentrated. The desired product was obtained in 68 % yield after purification by chromatography and recrystallization from hexane/EtOAc.

Example 60

2-(4-{[5-(benzyloxy)-3-(2-naphthoyl)-1H-indol-1-yl]methyl}phenyl)acetic acid

Step 1: Following step 1 of Example 59 using the appropriate acyl chloride yielded 42 % of the desired ketone after recrystallization from hexane/$CHCl_3$.

Step 2: An analogous procedure to step 2 of Example 59 yielded 35 % of the title compound after chromatographic purification and recrystallization from acetone/pentane.

Example 61

2-[4-({5-(benzyloxy)-3-[3,5-bis(trifluoromethyl)benzoyl]-1H-indol-1-yl}methyl)phenyl]acetic acid

Step 1: Following step 1 of Example 59 using the appropriate acyl chloride yielded 30 % of the desired ketone after recrystallization hexane/CH_2Cl_2/EtOAc.

Step 2: An analogous procedure to step 2 of Example 59 yielded 73 % of the title compound after chromatographic purification and recrystallization from $CHCl_3$/MeOH.

Example 62

4-({3-benzoyl-5-(benzyloxy)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step 1 The starting ethyl 5-benzyloxyindole-2-carboxylate (Scheme 21, step 1) was treated with LAH (1.3 eq) in THF (0.27 M) at 0 °C under nitrogen for 1 h. Workup with NaOH and water followed by concentration afforded crude product (100%).

Step 2 The crude alcohol from step 1 was dissolved in DMF (0.38 M), and treated with t-butyldimethylsilyl chloride (1.16 eq) and imidazole (1.26 eq) at 25 °C for 1 d. Workup and chromatographic purification afforded the pure product (93%).

Step 3 The silyl ether from step 2 was dissolved in methylene chloride (0.26 M), and treated with BOC anhydride (1.24 eq), triethylamine (1.53 eq) and DMAP (0.21 eq) at 25 °C for 3 d. Workup and chromatographic purification afforded the pure product (99%).

Step 4 The N-BOC silyl ether from step 3 was treated with acetic acid/ water/ THF (3:1:1) (0.04 M) at 25 °C for 1 d. Workup and chromatographic purification afforded the pure product (100%).

Steps 5 The alcohol from step 4 was dissolved in methylene chloride (0.2 M), and under nitrogen at -40°C treated with triethylamine (1.33 eq), and mesyl chloride (1.23 eq) for 1 h. In a separate dry flask was weighed naphthalene-2-thiol (1.31 eq), and THF (1 M) was added, followed by lithium hexamethyldisilazide (1N in THF, 1 eq) and this mixture was stirred at 25°C for 30 min. The resulting solution was then added dropwise, over 30 minutes, to the above mesylate solution, at -40°C. The reaction mixture was allowed to warm to 25°C, and stirred there for 4.5 h. Workup and chromatographic purification afforded the BOC thioether.

Step 6 The purified BOC thioether from step 5 was heated under nitrogen at 160-170°C for 1.25 h, and recrystallized from ethyl acetate and hexanes to afford the free indole thioether in 64% yield.

Step 7: The product of step 6 (1 eq) in CH_2Cl_2 (0.125 M) was ice cooled. A solution of MeMgBr (1.2 eq) in butyl ether (1 M) was added and the resulting mixture was stirred for 30 minutes. After warming up to 25°C, benzoyl chloride was added dropwise. The reaction was heated to reflux for 3 h, then stirred at 25°C overnight. After quenching with NH_4Cl, the mixture was extracted with CH_2Cl_2. Organic extracts were washed with brine, dried and concentrated. The desired ketone was obtained in 55 % yield after chromatographic purification.

Step 8: A solution of the product from step 1 (1 eq) in dry DMF (0.1 M) was treated with NaH (60 % in mineral oil, 1.05 eq). Methyl 4-bromomethylbenzoate (1.2 eq) was added after 1 h at 25°C and the resulting mixture was stirred overnight. EtOAc/water work up produced the desired crude material which was purified by chromatography (56 % yield).

Step 9: The material from step 2 (1 eq) was hydrolyzed by the action of $LiOH{\cdot}H_2O$ (1.2 eq) in THF/MeOH/water (3/1/1, 0.07 M). After stirring at 25°C overnight, the reaction mixture was quenched with AcOH and solvent was evaporated. EtOAc/water work up and chromatographic purification afforded the title compound in 78 % yield.

Example 63

4-({5-(benzyloxy)-3-isobutyryl-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step 1: Following step 7 of Example 62 using isopropyl chloride yielded the desired ketone after chromatography.

Step 2: An analogous procedure to step 8 of example 62 yielded 50 % of the N-alkylated material after chromatographic purification.

Step 3: Following step 9 of example 62 the methyl ester was hydrolyzed to the title compound in 67 % yield after chromatography.

Example 64

2-{3-acetyl-5-(benzyloxy)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}acetic acid

Step 2: The product of step 1 of Example 80 was alkylated with methyl bromoacetate following an analogous procedure to step 8 of example 62 to yield 65 % of the desired compound after recrystallization from EtOAc.

Step 3: Following step 9 of example 62 above the methyl ester was hydrolyzed to the title compound in 84 % yield after chromatography.

Example 65

2-{5-(benzyloxy)-3-isobutyryl-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}acetic acid

Step 2: An analogous procedure to step 2 of Example 63 started from methyl bromo acetate and the isopropyl ketone described in step 1 of Example 63 (step 1, see above). This reaction yielded 66 % of the N-alkylated material after chromatographic purification.

Step 3: Following step 3 of Example 63 the methyl ester was hydrolyzed to the title compound in 50 % yield after chromatography.

Example 66

4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoic acid

Step 1: A solution of EtMgBr in ether (3 N, 2.17 eq) was cooled to - 70°C. The product of step 2 in Example 62 (1 eq) in ether (0.55 M) was added and the reaction mixture was stirred at - 70°C for 2 h. After the addition of benzoyl chloride (3 eq) in ether (1.5 M) the reaction was stirred at - 40°C for 2 h, quenched with saturated $NaHCO_3$ at - 40°C and allowed to warm to 25°C. EtOAc/water work up and crystallization from hexane/EtOAc the desired ketone in 89 % yield.

Step 2: The material from step 1 (1 eq) in CH_2Cl_2 (0.25 M) was treated with NEt_3 (2 eq), followed by BOC anhydride (1.24 eq) and DMAP (0.21 eq). After stirring for 20 minutes at 25°C the reaction mixture was worked up with CH_2Cl_2 and water. Pure desired material was obtained in 97 % yield by trituration with hexane.

Step 3: The above material (1 eq) in THF (0.3 M) was combined with pyridine (excess) and HF·pyridine (excess) at 0°C. The reaction was stirred at 25°C for 1.5 h. EtOAc/water work up followed by chromatographic purification afforded the desired alcohol in 86 % yield.

Step 4: The alcohol from step 3 (1 eq) in CH_2Cl_2 (0.4 M) was treated with 2,6-lutidine (2.5 eq) followed by $SOCl_2$ (1.2 eq). After 30 minutes at 25°C the reaction was worked

up with EtOAc and water. The crude product was purified by chromatography and trituration with hexane to afford the corresponding chloride in 75 % yield.

Step 5: A mixture of the above material (1 eq), 325 mesh K_2CO_3 (2.4 eq), b-naphthol (1.2 eq) and KI (1.2 eq) in CH_3CN (0.3 M) was heated to reflux for 2 h. EtOAc/water work up, followed by trituration in hexane/EtOAc and chromatography of the mother liquor yielded 70 % of the expected ether.

Step 6: A NaOMe solution in MeOH was prepared by dissolving Na (3 eq) in MeOH (0.2 M). The product of step 5 (1 eq) in THF (0.04 M) was added and the reaction mixture was stirred at 25 °C for 3 h. EtOAC/water work up followed by trituration with hexane/EtOAc afforded the indole compound in 93 %.

Step 7: A solution of the product from step 6 (1 eq) in dry DMF (0.1 M) was treated with NaH (60 % in mineral oil, 1.1 eq). Methyl 4-bromobutyrate (1.2 eq) and KI (1.2 eq) were added after 1 h and the reaction mixture was stirred at 75°C for 3 h. EtOAc/water work up followed by chromatographic purification yielded 96 % of the required ester.

Step 8: The material from step 7 (1 eq) was hydrolyzed by the action of $LiOH \cdot H_2O$ (1.2 eq) in THF/MeOH/water (3/1/1, 0.2 M). After stirring at 25°C for 2 h, the reaction mixture was quenched with 1N HCl and extracted with EtOAc and CH_2Cl_2. The organic extracts were combined, washed, dried and concentrated. The crude material was purified by trituration in hexane/EtOAc to afford the title compound in 86 % yield.

Example 67

3-[(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]benzoic acid

Step 1: The product of Example 66 (1 eq) was reacted with EDCI (1.37 eq) and methyl 3-amino benzoate (1.05 eq) in DMF (0.09 M) in the presence of DMAP (0.2 eq). The reaction was stirred at 25°C for 1.5 h. EtOAc/water work up, followed by flash chromatography produced the desired amide in 81 % yield.

Step 2: An analogous procedure to step 2 of Example 66 yielded 98 % of the title compound after purification by trituration in hexane/EtOAc.

Example 68

4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-N-[3-({[(trifluoromethyl)sulfonyl]amino}carbonyl)phenyl]butanamide

Step 1: Following step 1 of Example 67 and using the acid of Example 67 and the appropriate sulfonamide provided after overnight reaction and analogous work up the desired product. Trituration with hexane/EtOAc yielded 100 % of the title compound.

Example 69

4-[(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]benzoic acid

Step 1: Following step 1 of Example 67 above using acid of Example 66 and the appropriate aniline yielded 76 % of the expected amide.

Step 2: An analogous procedure to step 2 of Example 67 yielded 78 % of the title compound after purification by trituration in hexane/EtOAc.

Example 70

2-[(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]benzoic acid

Step 1: Following step 1 of Example 67 using acid of Example 66 and the appropriate aniline yielded 36 % of the expected amide after chromatography.

Step 2: An analogous procedure to step 2 of Example 67 yielded 67 % of the title compound after purification by trituration in hexane/EtOAc.

Example 71

3-[(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]propanoic acid

Step 1: Following step 1 of Example 67 using acid of Example 66 and the appropriate aniline yielded 96 % of the expected amide after chromatography.

Step 2: An analogous procedure to step 2 of Example 67 yielded 90 % of the title compound after purification by trituration in hexane/EtOAc.

Example 72

3-[(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]propanoic acid

Following step 1 of Example 67 using acid of Example 66 and the appropriate sulfonamide yielded 100 % of the title compound.

Example 73

N-(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)-2-methylbenzenesulfonamide

Following step 1 of Example 67 using acid of Example 66 and the appropriate sulfonamide yielded 80 % of the title compound after chromatography.

Example 74

5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}pentanoic acid

Step 1: A solution of the product from step 6 of Example 66 (1 eq) in dry DMF (0.1 M) was treated with NaH (60 % in mineral oil, 1.1 eq). Ethyl 4-bromopentanoate (1.2 eq) and KI (1.2 eq) were added after 1 h and the reaction mixture was stirred at 75°C for 2 h. EtOAc/water work up followed by chromatographic purification yielded 92 % of the required ester.

Step 2: The material from step 1 (1 eq) was hydrolyzed by the action of $LiOH{\cdot}H_2O$ (1.3 eq) in THF/MeOH/water (3/1/1, 0.2 M). After stirring at 25°C for 3.5 h, the reaction mixture was quenched with 1N HCl and extracted with EtOAc and CH_2Cl_2. The organic extracts were combined, washed, dried and concentrated. The crude material was purified by trituration in hexane/EtOAc to afford the title compound in 95 % yield.

Example 75

3-[(5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}pentanoyl)amino]benzoic acid

Step 1: The acid of Example 74 (1 eq) was reacted with EDCI (1.37 eq) and methyl 3-amino benzoate (1.05 eq) in DMF (0.09 M) in the presence of DMAP (0.2 eq). The reaction was stirred at 25°C for 2.5 h. EtOAc/water work up, followed by flash chromatography produced the desired amide in 78 % yield.

Step 2: An analogous procedure to step 2 of Example 74 yielded 83 % of the title compound after purification by trituration in hexane/EtOAc.

Example 76

5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-N-[3-({[(trifluoromethyl)sulfonyl]amino}carbonyl)phenyl]pentanamide

Step 1: Following step 1 of Example 68 using acid of Example 75 and the appropriate sulfonamide yielded 83 % of the title compound after overnight reaction and analogous work up.

Example 77

2-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}acetic acid

Step 1: Following step 1 of Example 74 using the appropriate bromide yielded 80 % of the expected amide after chromatography.

Step 2: An analogous procedure to step 2 of Example 74 yielded 90 % of the title compound after trituration in hexane/EtOAc.

Example 78

(E)-4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-2-butenoic acid

Step 1: Following step 1 of Example 74 using the appropriate bromide yielded 33 % of the expected amide after chromatography.

Step 2: An analogous procedure to step 2 of Example 74 yielded 70 % of the title compound after trituration in hexane/EtOAc.

Example 79

3-({3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}methyl)benzoic acid

Step 1: Following step 1 of Example 74 using the appropriate bromide yielded 75 % of the expected amide after chromatography.

Step 2: An analogous procedure to step 2 of Example 74 yielded 92 % of the title compound after trituration in hexane/EtOAc.

Example 80

1-{1-[4-(1,3-benzothiazol-2-ylcarbonyl)benzyl]-5-(benzylsulfanyl)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-3-yl}-1-ethanone

Step 1 The thioether from step 6, Example 62 was dissolved in methylene chloride (0.12 M), and under nitrogen at 0°C treated with methylmagnesium bromide (1.1 eq), and stirred at 0 to 25°C for 1 h. The mixture was recooled to 0°C and acetyl chloride (1.17 eq) was added. After 1 h at 0°C, the reaction mixture was quenched by addition of half saturated ammonium chloride solution, and worked up with methylene chloride. Chromatographic purification afforded the pure product (37%).

Step 2 Following the procedure for Example 81 step 1 and using p-Toluoyl chloride yielded the corresponding para amide.

Step 3 Following the procedure for Example 81 step 2 and using the product from step 1 above, the desired product was obtained.

Step 4 Following the procedure for step 3, Example 81 and using the material from step 3 yielded the desired benzyl bromide.

Step 5 Following the procedure for Example 81 step 4, the material from step 4 was coupled to the material from step 1 to yield the titled compound.

Example 81

1-{1-[3-(1,3-benzothiazol-2-ylcarbonyl)benzyl]-5-(benzylsulfanyl)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-3-yl}-1-ethanone

Step 1 m-Toluoyl chloride (0.8 M) was added to triethylamine (2.44 eq) and methoxymethyl amine HCl (1.1 eq) dissolved in methylene chloride at 0°C over 20 min. The reaction was allowed to warm to 25°C. After stirring at 25°C for 1 day, workup with methylene chloride and water afforded crude product in ca. 100% yield.

Step 2 Under anhydrous conditions benzothiazole was dissolved in THF (0.35 M). At -78 °C added BuLi (1.1 eq). After 1 h at -78°C, added the amide from step 1 in THF, over 15 min. The reaction was allowed to warm to 25°C. After stirring at 25°C for 1 day, workup with ethyl acetate and water and chromatography afforded pure tolyl ketone product (52%).

Step 3 The tolyl ketone from step 2 was dissolved in carbon tetrachloride (0.19M), and NBS (1.2 eq) and AIBN (0.11 eq) were added. After 1 d at 60°C, about 1:1 of starting material and product were present. Resubmission under the same conditions, followed by filtration and recrystallization from ethyl acetate afforded pure bromobenzyl ketone product (28%).

Step 4 The indole from step 1 of Example 80 was dissolved in dry DMF (0.04 M), followed by NaH (1.25 eq). After 45 min at 25°C, added the bromobenzyl ketone from step 3 (1.25 eq), and stirred for 1 h at 25°C. Workup, chromatography, and recrystallization from ethyl acetate/hexanes afforded the pure title compound (45%).

Example 82

2-[3-({3-acetyl-5-(benzyloxy)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoyl]-1,3-benzothiazole-6-carboxylic acid

Step1 Ethyl 4-aminobenzoate was dissolved in 95% v/v HOAc/water (0.4 M) and at 25 °C treated with sodium thiocyanate (4.1 eq), and stirred at 25°C for 20 min. The mixture was cooled to 5°C and bromine (1.17 eq) in 95% v/v HOAc/water was added. After 1 h at 0 _C, the reaction mixture was quenched by addition of water, and filtered. Workup (ethyl acetate and sodium bicarbonate solution) gave 81% of the pure thiocyanate product.

Step 2 The aryl thiocyanate from step 1 was treated with sodium sulfide nonahydrate dissolved in water (1.2 eq, 1.3 M), and heated at reflux for 45 min. The cooled mixture was filtered, acidified to pH = 6 with HOAc, extracted with ethyl acetate, and concentrated to give the thiophenol product (91%).

Step 3 The thiophenol from step 2 was dissolved in 90% v/v HCOOH/water (3.3 M), and zinc dust (cat.) was added. After 3 h at reflux, workup with ethyl acetate and alkali afforded pure benzothiazole ester (60%).

Step 4 Benzothiazole ester (step 3) was dissolved in THF/methanol/water (8:3:3), (0.34 M), lithium hydroxide (2 eq) was added, and the mixture was stirred for 2 h at 25°C. Workup (ethyl acetate/ aqueous acid) afforded pure benzothiazole acid (100%).

Step 5 Under anhydrous conditions the benzothiazole acid (step 4) was dissolved in THF (0.052 M). At -78°C added BuLi (2.2 eq). After 1 h at -78°C to 0°C, added the amide (1.28 eq) from step 1 of Example 81, in THF, at -78°C, over 5 min.

After 0.5 h at -78°C, the reaction was allowed to warm to 25°C. After stirring at 25°C for 2h, workup with ethyl acetate and water and chromatography afforded pure tolyl ketone acid product (64%).

Step 6 The tolyl ketone acid from step 5 was suspended in (1:1) THF/ethanol, (0.075 M), and conc. sulfuric acid (excess) was added. After reflux for 1 d, workup (ethyl acetate and sodium bicarbonate solution) and purification by chromatography gave the pure tolyl ketone ester product (69%).

Step 7 The tolyl ketone ester from step 6 was dissolved in carbon tetrachloride (0.05M), and NBS (1.2 eq) and AIBN (0.15 eq) were added. After 1.25 h at reflux, another portion of NBS (0.3 eq) and AIBN (0.07 eq) were added. Filtration and recrystallization from ethyl acetate afforded pure bromobenzyl ketone product (22%).

Step 8 The indole from step 1 of Example 80 was dissolved in dry DMF (0.06 M), followed by NaH (1.11 eq). After 45 min at 25°C, added the bromobenzyl ketone from step 7 above (1.25 eq), and stirred for 1 h at 25°C. Workup afforded the crude ester, used in the next step.

Step 9 The crude ester from step 8 was dissolved in THF/methanol/water (8:2:2), (0.013 M), lithium hydroxide (4.3 eq) was added in portions, as the mixture was stirred for a total of 3-4 d at 25°C. Workup (ethyl acetate/ aqueous HCl) and purification by chromatography afforded pure benzothiazole acid (31%).

Example 83

5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-2-oxopentanoic acid

Step 1 The indole from step 6 of Example 66 was dissolved in dry DMF (0.17 M), followed by NaH (1.2 eq). After 1.5 h at 25°C, added 3-iodo-1-chloropropane, and stirred for 4 h at 25°C. Workup (ethyl acetate/bicarbonate solution) and trituration (ethyl acetate/hexanes) afforded the product in 89% yield.

Step 2 The alkyl chloride from step 1 was dissolved in methyl ethyl ketone (0.036 M), followed by NaI (1.6 eq). After stirring for 1 d at reflux in the dark, workup (ethyl acetate/water) afforded the product iodide in 97% yield.

Step 3 NaH (1.0 eq) was weighed into a dry flask under nitrogen, and dry benzene (0.14 M) was added. At 0°C, added dry DMF (0.4 M), ethyl 2-carboxy-1,3-dithiane (1.0 eq), and the iodide from step 2 (1.0 eq) into a separate dry flask. This DMF solution was then added at 0°C to the benzene suspension, and the mixture was allowed to warm to 25°C and stirred for 3 h at 25°C. Workup (ethyl acetate/water) and chromatography afforded the product dithianyl ester in 54% yield.

Step 4 Silver nitrate (4.5 eq) and NCS (4.0 eq) were dissolved in 4:1 v/v acetonitrile/water (ca. 0.04 M), and a solution of the dithianyl ester from step 3 (1 eq) in acetonitrile (0.03 M) was added at 25°C. After stirring for 5 min at 25°C, added a sodium sulfite solution, followed in one minute by a sodium carbonate solution. Workup (ethyl acetate/water) and chromatography afforded the product ketoester in 17% yield.

Step 5 The ketoester from step 4 was dissolved in THF/water (8:1), (0.03 M), lithium hydroxide (1.5 eq) was added, and the mixture was stirred for 2 h at 25°C. Workup (ethyl acetate/ aqueous HCl) and purification by chromatography afforded pure ketoacid (64%).

Example 84

3-[(5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-2-oxopentanoyl)amino]benzoic acid

Step 1 The dithianyl ester from step 3 Example 83 was dissolved in THF/ethanol/water (5:2:2) (0.008 M), and lithium hydroxide (11 eq) was added, and the mixture was stirred for 1 d at 50°C. Workup (ethyl acetate/ aqueous HCl) and chromatography afforded the pure dithianyl acid (90%).

Step 2 The dithianyl acid from step 1 was dissolved in dry methylene chloride (0.08 M), and DMF (cat.). Oxalyl chloride (1.2 eq) was added, and the reaction was stirred at 25°C for 0.5 h. Concentration was followed by redissolution in dry methylene chloride, and addition , at 0°C, of methyl 3-aminobenzoate (1.05 eq) and triethylamine (1.0 eq). The reaction was warmed to 25 °C, and stirred there for 3 h. Workup (ethyl acetate/aqueous acid) and purification by chromatography afforded the product dithianyl ester in 89% yield.

Step 3 The dithianyl ester from step 2 was dissolved in THF/methanol/water (6:4:3) (0.02 M), and lithium hydroxide (4.3 eq) was added, and the mixture was stirred

for 3 h at 25°C. Workup (ethyl acetate/ aqueous HCl) afforded the dithianyl acid (R = 3-COOH) (91%).

Step 4 Silver nitrate (4.6 eq) and NCS (4.0 eq) were dissolved in 4:1 v/v acetonitrile/water (ca. 0.03 M), and a solution of the dithianyl acid from step 3 (1 eq) in acetonitrile (0.009 M) was added at 25°C. After stirring for 10 min at 25°C, there was added a sodium sulfite solution, followed in one minute by a sodium carbonate solution. Workup (ethyl acetate/aqueous acid) and chromatography afforded the title compound in 82% yield.

Example 85

4-[(5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-2-oxopentanoyl)amino]benzoic acid

Step 1 The dithianyl acid from step 1 Example 84 was treated as described above for step 2 Example 84 except ethlyl 4-aminobenzoate was substituted. Purification by chromatography afforded the product dithianyl ester (R = 4-$COOC_2H_5$) in 30% yield.

Step 2 The dithianyl ester from step 1 was treated as described for step 3 of Example 84. Purification by chromatography afforded the product dithianyl acid (R = 4-COOH) in 89% yield.

Step 3 The dithianyl from step 6 was treated as described for step 4 of Example 84. Repeated purification by chromatography followed by trituration in pentane afforded the title compound in 30 % yield.

Example 86

Table I reports data for the compounds described in the examples above in cPLA2 inhibition assays (described below). In the data columns of the tables, assay results are reported as an "IC_{50}" value, which is the concentration of a compound which inhibits 50% of the activity of the phospholipase enzyme in such assay. Where no numerical IC_{50} value appears, "NA" denotes that inhibitory activity was not detected from such compound in the corresponding assay and a blank box denotes that the compound was not tested in such assay as of the time of filing of the present application.

Activity Assays

(a) Vesicle Assay

1-palmitoyl-2-[^{14}C] arachidonyl phosphotidylcholine (58 mCi/mmol) (final concentration 6 M) and 1,2-dioleyolglycerol (final concentration 3 M) were mixed and dried under a stream of nitrogen. To the lipids was added 50 mM Hepes pH 7.5 (2x final concentration of lipids) and the suspension was sonicated for 3 min. at 4°C. To the suspension was added 50 mM Hepes pH 7.5, 300 mM NaCl, 2 mM DTT, 2 mM $CaCl_2$ and 2 mg/ml bovine serum albumin (BSA) (Sigma A7511) (1.2x final concentration of lipids). A typical assay consisted of the lipid mixture (85 l) to which was added consecutively, the inhibitor (5 l in DMSO) and $cPLA_2$, 10 ng for an automated system or 1 ng for a manual assay, in 10l of the BSA buffer. This assay was conducted by either the manual assay or automated assay protocol described below.

(b) Soluble Substrate Assay (LysoPC)

1-[^{14}C]-palmitoyl-2-hydroxyphosphotidyl-choline (57 mCi/mmol) (final concentration 4.4 M) was dried under a stream of nitrogen. The lipid was resuspended by vortexing 80 mM Hepes pH 7.5, 1 mM EDTA (1.2 x final concentration). A typical assay consisted of lipid suspension (85 l) to which was added consecutively the inhibitor (5l in DMSO) and $cPLA_2$, 200 ng in 80 mM Hepes pH 7.5, 2 mM DTT and 1 M EDTA. This assay was conducted by either the manual assay or automated assay protocol described below.

(c) Automated Assay

The lipid suspension and inhibitor were pre-incubated for 7 min. at 37°C. Enzyme was added and the incubation was continued for a further 30 mins. The reaction was then quenched by the addition of decane: isopropanol: trifluoroacetic acid (192:8:1 w/v, 150 l). A portion of the quench layer (50 l) was passed through a Rainin Spheric-5 silica column (5, 30 x 2.1 mm) eluting with heptane:methanol:TFA (97:3:0.1 v/v). The level of [^{14}C]-arachidonic acid was analyzed by an in-line Radiomatic Flo-One/Beta counter (Packard).

(d) Manual Assay

The lipid, inhibitor and enzyme mixture were incubated at 37°C for 30 min. The reaction was quenched by the addition of heptane:isopropanol:0.5M sulfuric acid (105:20:1 v/v, 200 l). Half of the quench layer was applied to a dispoable silica gel column (Whatman SIL, 1 ml) in a vacuum manifold positioned over a scintillation vial. Free [^{14}C]- arachidonic acid was eluted by the addition of ethyl ether (1 ml). The level of radioactivity was measured by liquid scintillation counter.

(e) PMN Assay

PMNs were isolated using Ficoll-Hypaque according to the manufacturers directions. Red blood cells contaminating the PMNs were removed by hypotonic lysis, and the PMN pellet was washed once, and resuspended in Hanks buffered saline at a concentration of 2 x 10^6 cells/ml. The cells were preincubated with inhibitors for 15 min at 37%C and then stimulated with 2 uM A23187. When monitoring LTB_4 production as a measure of $cPLA_2$ inhibition, the reaction was quenched with an equal volume of ice cold phosphate buffered saline. Cells were removed by centrifugation, and the LTB_4 present in the cell supernatant was measured using the LTB_4 scintillation proximity assay provided by Amersham according to the manufacturers directions. In the assays reported in the Tables above, LTB_4 was measured. When monitoring arachidonic acid production, the reaction was quenched with methanol containing D8-arachidonic acid as an internal reference. The lipids were extracted by the method of Bligh et al. ((1959) Can. J. Biochem. Physiol., 37, 911-917), and the fatty acid was converted to the pentafluorobenzyl ester and analyzed by GC-MS in a manner similar to that reported by Ramesha and Taylor ((1991) *Anal. Biochem.* 192, 173-180).

(f) RBL Assay

RBL-2H3 cells were routinely cultured as 37°C in a 5% CO_2 atmosphere in minimal essential medium containing nonessential amino acids and 12% fetal calf serum. The day before the experiment, cells were seeded into spinner flasks at 3 x 10^5 cells/ml and 100 ng/ml DNP specific-IgE was added. After 20 hrs, the cells were harvested by centrifugation and washed once in serum-free minimal essential media, and resuspended to 2 x 10^6 cells/ml in serum free media. The cells were then preincubated with either inhibitor in DMSO (1% v/v) or DMSO (1% v/v) for 15 min at 37°C followed by stimulation with DNP-BSA (300 ng/ml). After 6 min, the cells were removed by centrifugation, and the supernatant was assayed for PGD_2 content in accordance with known methods.

(g) Coumarine Assay

7-hydroxycoumarinyl 6-heptenoate was used as a monomeric substrate for cPLA2 as reported previously (Huang, Z. et al., 1994, Nalytical Biochemistry 222, 110-115). Inhibitors were mixed with 200 μL assay buffer (80 mM Heped, pH 7.5, 1 mM EDTA) containing 60 μM 7-hydroxycoumarinyl 6-heptenoate. The reaction was initiated by adding 4 μg cPLA2 in 50 μL assay buffer. Hydrolysis of the 7-hydroxycounarimyl 6-heptenoate ester was monitored in a fluorometer by exciting at 360 nm and monitoring emission at 460 nm. Enzyme activity is proportional to the increase in emission at 460 nm per minute. In the presence of a cPLA2 inhibitor, the rate of increase is less.

Example 87

Compounds of the present invention were also tested for *in vivo* activity in a rat paw edema test according to the procedure described below. The results are reported in Table II.

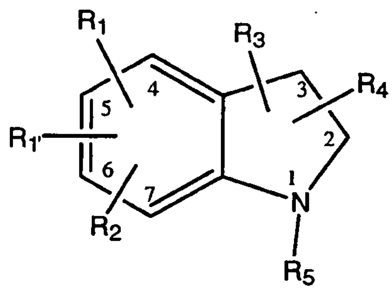
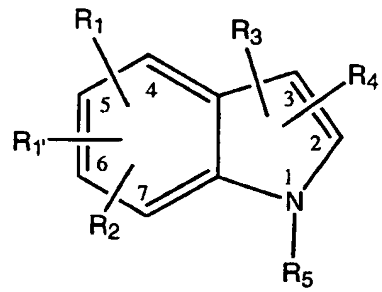
Rat Carrageenan-Induced Footpad Edema Test

Each compound was suspended in 0.3ml absolute ethanol, 0.1 ml Tween-80 and 2.0 ml Dulbecco's PBS (without calcium or magnesium). To this mixture, 0.1ml 1N NaOH was added. After solution was complete, additional amounts of PBS were added to adjust the concentration to 1 mg/ml. All comounds remained in solution. Compounds were administered i.v. in a volumne of 5 ml/kg to male Sprague Dawley rats at the same time that edema was induced by injection of 0.05ml of 1% Type IV carrageenan into the hind footpad. Footpad volume was measured before dosing with compound and 3 hours after dosing with carageenan.

All patent and literature references cited herein are incorporated as if fully set forht herein.

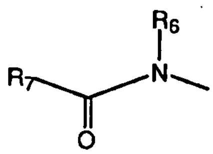
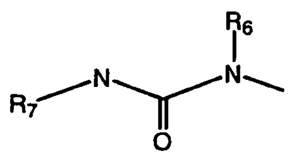
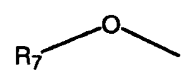
What is claimed is:

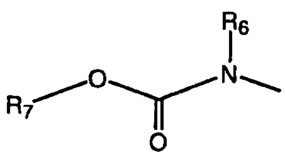
1. A compound of the formulae:

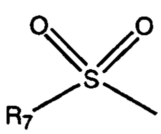
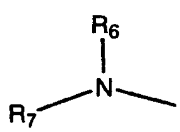
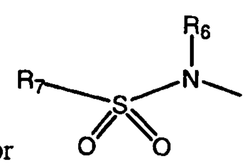
 or 

wherein:

R_1 and $R_{1'}$ are independently selected from H, halogen, $-CF_3$, -OH, $-C_1-C_{10}$ alkyl, -S-C_1-C_{10} alkyl, C_1-C_{10} alkoxy, -CN, $-NO_2$, $-NH_2$, $-HN(C_1-C_6)$, $-N(C_1-C_6)_2$, phenyl, -O-phenyl, -S-phenyl, benzyl, -O-benzyl, -S-benzyl or a moiety of the formulae:

 ,  ,  ,

 ,

 ,  , or  ;

R_6 is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, -O-phenyl, benzyl, -O-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, -CN, -CF_3, or -OH;

R_7 is selected from -OH, $-CF_3$, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NH-(C_1-C_6 alkyl), -N-(C_1-C_6 alkyl)$_2$, pyridinyl, thienyl, furyl, pyrrolyl, phenyl, -O-phenyl, benzyl, -O-benzyl, the rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, $-CF_3$, or -OH;

R_2 is selected from H, halogen, $-CF_3$, -OH, -C_1-C_{10} alkyl, C_1-C_{10} alkoxy, -CHO, -CN, $-NO_2$, $-NH_2$, -NH-C_1-C_6 alkyl, -N(C_1-C_6 alkyl)$_2$, -N-SO_2-C_1-C_6 alkyl, or -SO_2-C_1-C_6 alkyl;

R_3 is selected from H, $-CF_3$, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, C_3-C_{10} cycloalkyl, -C_1-C_6 alkyl-C_3-C_{10} cycloalkyl, -CHO, halogen, or a moiety of the formula -L^2-M^2:

L^2 indicates a linking or bridging group of the formulae -$(CH_2)_n$-, -S-, -O-, -C(O)-, -$(CH_2)_n$-C(O)-, -$(CH_2)_n$-C(O)-$(CH_2)_n$-, -$(CH_2)_n$-O-$(CH_2)_n$-, or -$(CH_2)_n$-S-$(CH_2)_n$-, -C(O)C(O)X;
where X = O,N

M^2 is selected from the group of C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, C_3-C_{10} cycloalkyl, phenyl or benzyl, the cycloalkyl, phenyl or benzyl rings being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, $-NO_2$, $-NH_2$, -CN, or $-CF_3$; or

a) a five-membered heterocyclic ring containing one or two ring heteroatoms selected from N, S or O including, but not limited to, furan, pyrrole, thiophene, imidazole, pyrazole, pyrrolidine, or tetrazole, the five-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, $-NO_2$, $-NH_2$, -CN, or $-CF_3$; or

b) a six-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, S or O including, but not limited to pyridine, pyrimidine, piperidine, piperazine, or morpholine, the six-membered heterocyclic ring being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, -CHO, $-NO_2$, $-NH_2$, -CN, $-CF_3$ or -OH; or

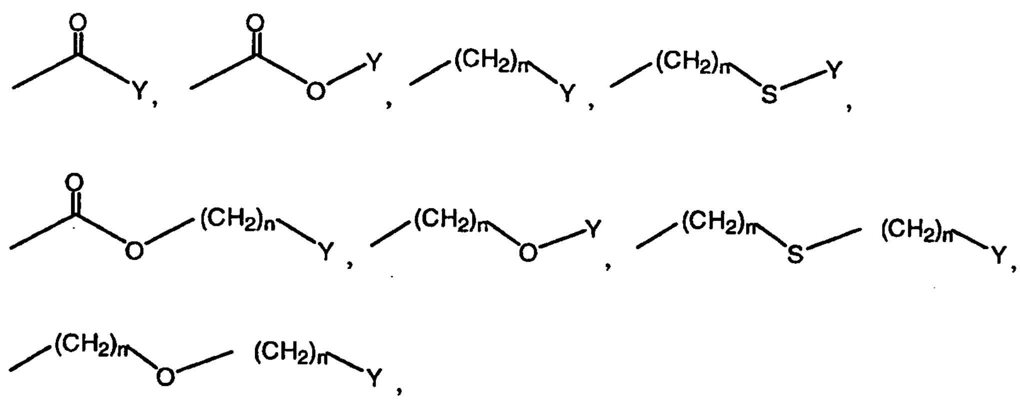
c) a bicyclic ring moiety containing from 8 to 10 ring atoms and optionally containing from 1 to 3 ring heteroatoms selected from N, S or O including, but not limited

to benzofuran, indole, indoline, napthalene, purine, or quinoline, the bicyclic ring moiety being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, -CHO, $-NO_2$, $-NH_2$, -CN, $-CF_3$ or -OH;

n is an integer from 0 to 3;

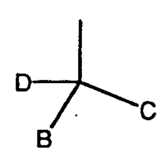
R_4 is selected from the group of C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, $-(CH_2)_n$-C_3-C_6 cycloalkyl, $-(CH_2)_n$-S-$(CH_2)_n$-C_3-C_5 cycloalkyl, $-(CH_2)_n$-O-$(CH_2)_n$-C_3-C_5 cycloalkyl, or the groups of:

a) $-(CH_2)_n$-phenyl-O-phenyl, $-(CH_2)_n$-phenyl-CH_2-phenyl, $-(CH_2)_n$-O-phenyl-CH_2-phenyl, $-(CH_2)_n$-phenyl-(O-CH_2-phenyl$)_2$, $-CH_2$-phenyl-C(O)-benzothiazole or a moiety of the formulae:



wherein n is an integer from 0 to 3, Y is C_3-C_5 cycloalkyl, phenyl, benzyl, napthyl, pyridinyl, quinolyl, furyl, thienyl or pyrrolyl; rings of these groups being optionally substituted by from 1 to 3 substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NH_2$, $-NO_2$ or a five membered heterocyclic ring containing one heteroatom selected from N, S, or O; or

b) a moiety of the formulae $-(CH_2)_n$-A, $-(CH_2)_n$-S-A, or $-(CH_2)_n$-O-A, wherein A is the moiety:

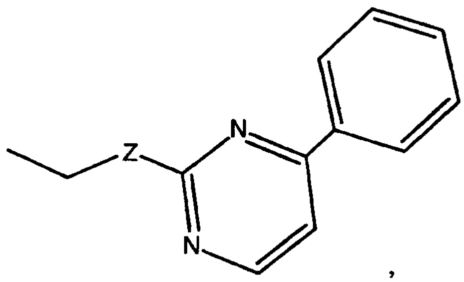


wherein

D is H, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, or $-CF_3$;

B and C are independently selected from phenyl, pyridinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, substituents selected from H, halogen, $-CF_3$, -OH, $-C_1-C_6$ alkyl, C_1-C_6 alkoxy, or $-NO_2$; or

c) a moiety of the formulae:



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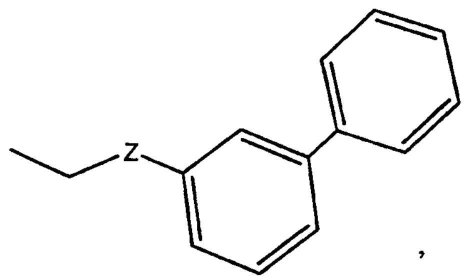

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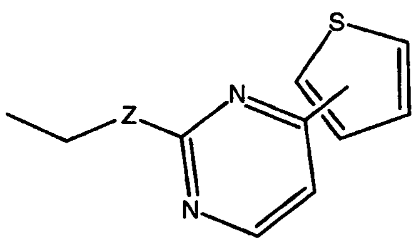

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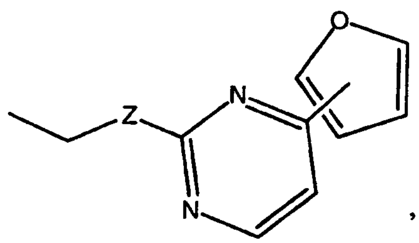

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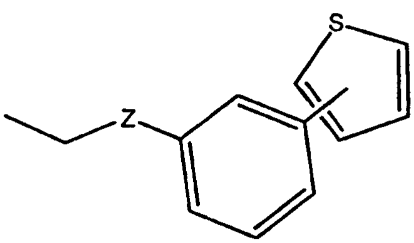

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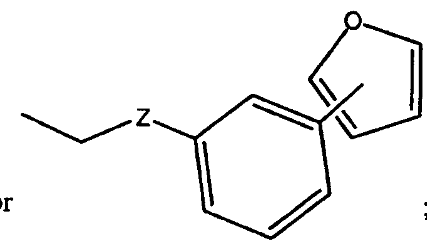
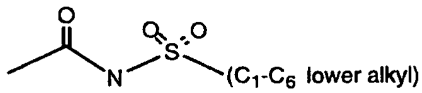
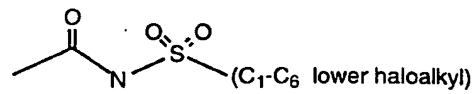


;

wherein Z is O or S and the phenyl and pyrimidinyl rings of each moiety are optionally and independently substituted by from 1 to 3 substituents selected from halogen, $-CF_3$, -OH, $-C_1-C_6$ alkyl, C_1-C_6 alkoxy, $-NH_2$, or $-NO_2$;

R_5 is selected from -COOH, -C(O)-COOH, $-(CH_2)_n$-C(O)-COOH, $-(CH_2)_n$-COOH, -CH=CH-COOH, $-(CH_2)_n$-tetrazole,

or 

or 

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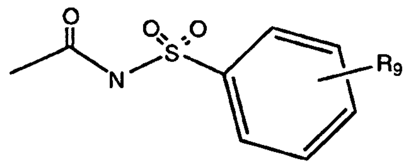

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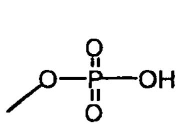
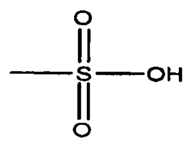
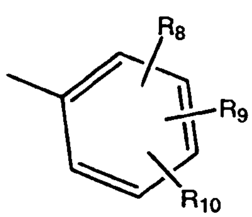


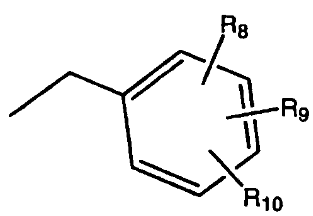
or 

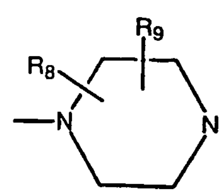
or a moiety selected from the formulae $-L^1-M^1$;

wherein L^1 is a bridging or linking moiety selected from a chemical bond, $-(CH_2)_n-$, -S-, -O-,
-C(O)-, $-(CH_2)_n-C(O)-$, $-(CH_2)_n-C(O)-(CH_2)_n-$, $-(CH_2)_n-O-(CH_2)_n-$,$-(CH_2)_n-S-(CH_2)_n-$, $-C(Z)-N(R_6)-$, $-C(Z)-N(R_6)-(CH_2)_n-$, $-C(O)-C(Z)-N(R_6)-$, $-C(O)-C(Z)-N(R_6)-(CH_2)_n-$, $-C(Z)-NH-SO_2-$, or $-C(Z)-NH-SO_2-(CH_2)_n-$;

M^1 is selected from the group of -COOH, $-(CH_2)_n-COOH$, $-(CH_2)_n-C(O)-COOH$, tetrazole,



, 

, 

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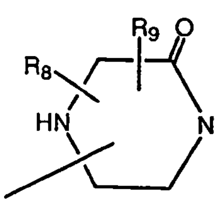
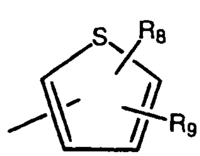
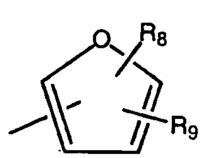
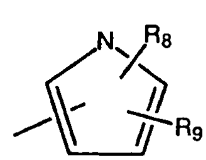


, 

, 

, 

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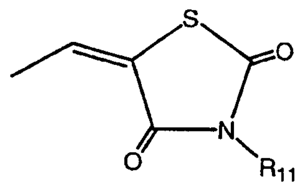
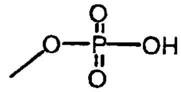
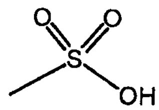
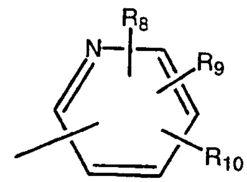
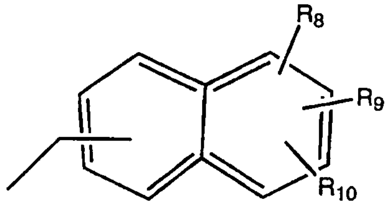
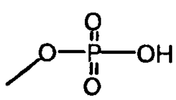
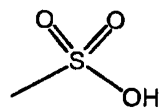
, ,  or 



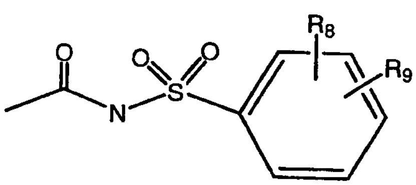
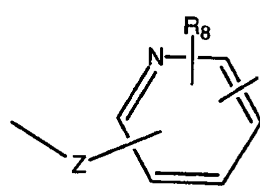
where R_8, R_9 or R_{10} can be attatched anywhere in the cyclic or bicyclic system,

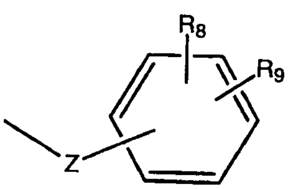
R_8, in each appearance, is independently selected from H, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, tetrazole,

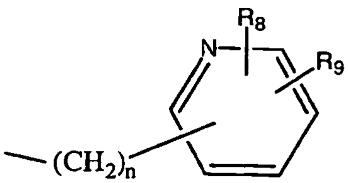
, or ;

R_9 is selected from H, halogen, -CF_3, -OH, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), or -N(C_1-C_6 alkyl$)_2$;

R_{10} is selected from the group of H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl$)_2$,

, ,

,



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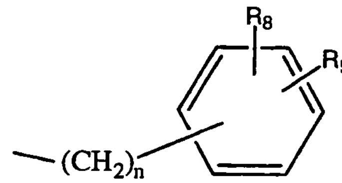

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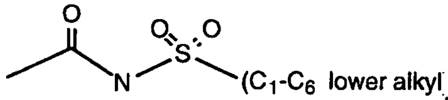

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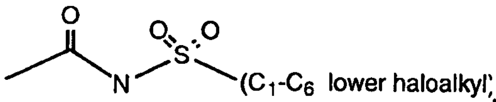

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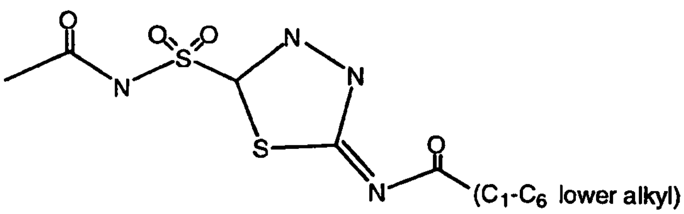

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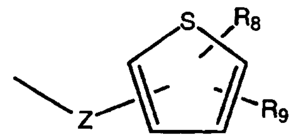

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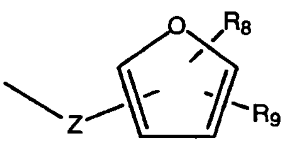

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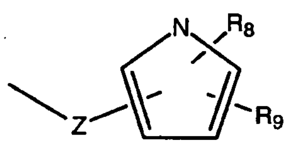

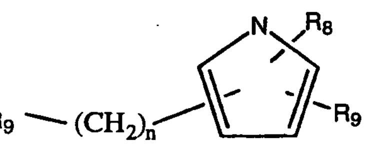

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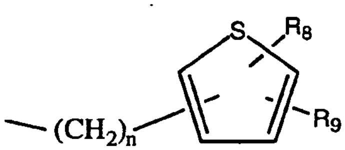

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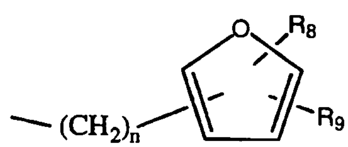
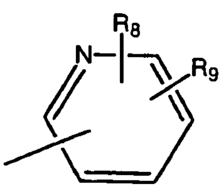


;

R_{11} is selected from H, C_1-C_6 lower alkyl, C_1-C_6 cycloalkyl, $-CF_3$, -COOH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH,



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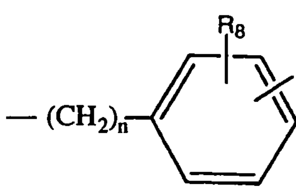
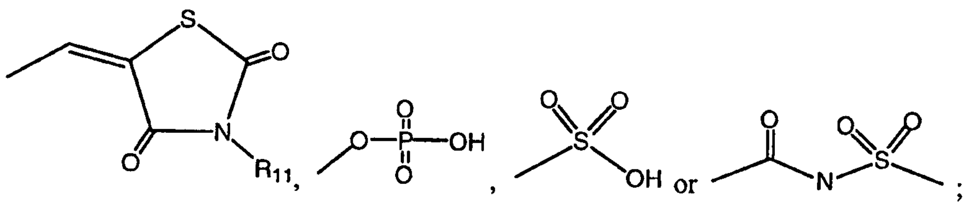


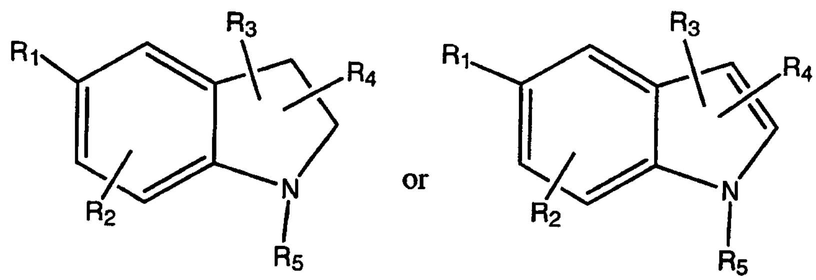
;

with a proviso that the complete moiety at the indole or indoline 1-position created by any combination of R_5, R_8, R_9, R_{10}, and/or R_{11} shall contain at least one acidic moiety selected from or containing a carboxylic acid, a tetrazole, or a moiety of the formulae:



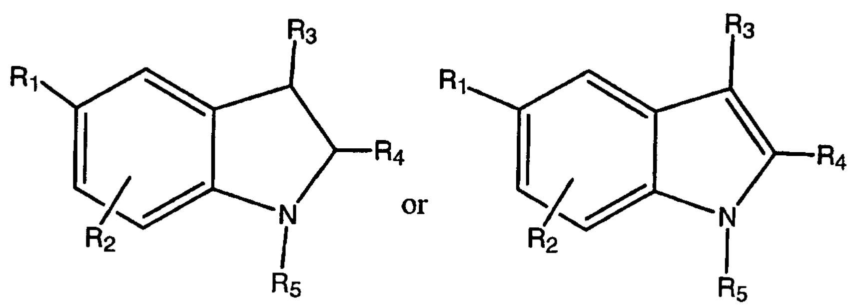
n is an integer from 0 to 3;
or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 having the formula:



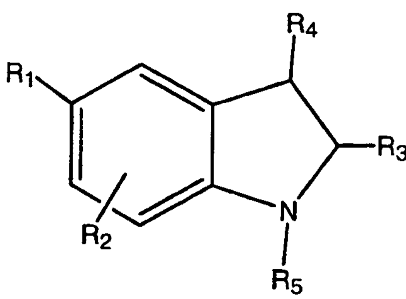
wherein R_3 is hydrogen and R_1, R_2, R_4, and R_5 are as described in Claim 1, or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 2 having the formula:

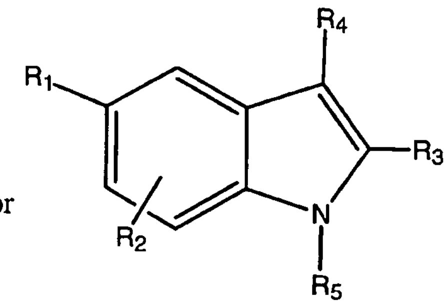


wherein R_1, R_2, R_3, R_4, and R_5 are as described in Claim 2, or a pharmaceutically acceptable salt thereof.

4. A compound of Claim 2 having the formula:

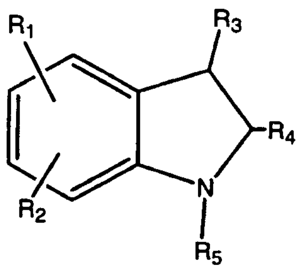


or

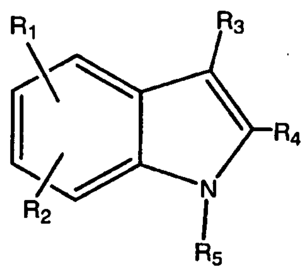


wherein R_1, R_2, R_3, R_4, and R_5 are as described in Claim 2, or a pharmaceutically acceptable salt thereof.

5. A compound of the formulae:

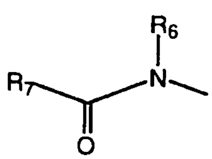


or



wherein:

R_1 is selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, $-HN(C_1$-$C_6)$, $-N(C_1$-$C_6)_2$, phenyl, -O-phenyl, benzyl, -O-benzyl, or a moiety of the formulae:



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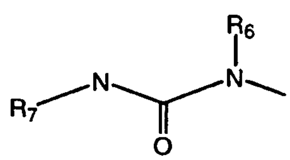

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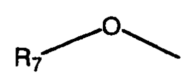

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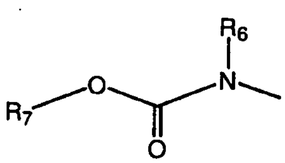

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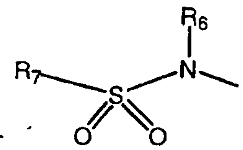
or  ;

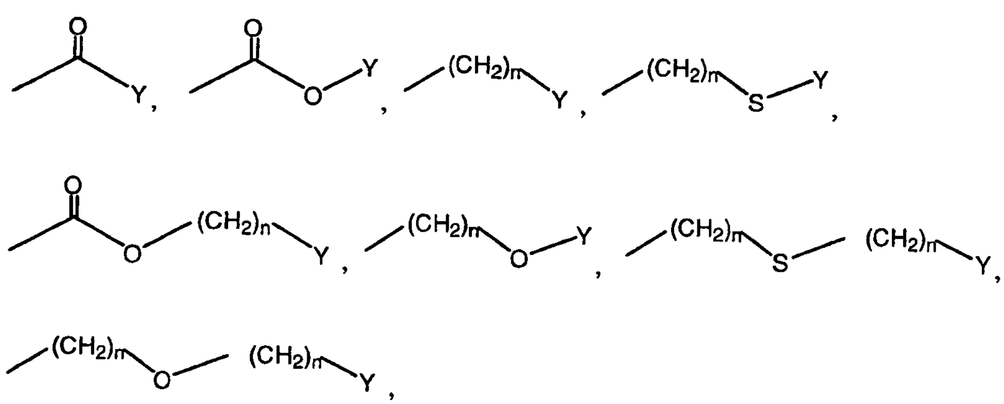
R_6 is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, -O-phenyl, benzyl, -O-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NH_2$, $-NO_2$, $-CF_3$, or -OH;

R_7 is selected from $-(CH_2)_n$-COOH, $-(CH_2)_n$-N-(C_1-C_6 alkyl)$_2$, $-(CH_2)_n$-NH-(C_1-C_6 alkyl), $-CF_3$, C_1-C_6 alkyl, C_3-C_5 cycloalkyl, C_1-C_6 alkoxy, -NH-(C_1-C_6 alkyl), -N-(C_1-C_6 alkyl)$_2$, pyridinyl, thienyl, furyl, pyrrolyl, phenyl, -O-phenyl, benzyl, -O-benzyl, adamantyl, or morpholinyl, the rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NH_2$, $-NO_2$, $-CF_3$, or -OH;

R_2 is selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_{10} alkyl, C_1-C_{10} alkoxy, -CHO, -CN, $-NO_2$, $-NH_2$, -NH-C_1-C_6 alkyl, -N(C_1-C_6 alkyl)$_2$, -N-SO_2-C_1-C_6 alkyl, or $-SO_2$-C_1-C_6 alkyl;

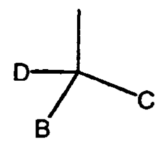
R_3 is selected from the group of C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, $-(CH_2)_n$-C_3-C_6 cycloalkyl, $-(CH_2)_n$-S-$(CH_2)_n$-C_3-C_6 cycloalkyl, or the groups of:

a) $-(CH_2)_n$-phenyl-O-phenyl, $-(CH_2)_n$-phenyl-CH_2-phenyl, $-(CH_2)_n$-O-phenyl-CH_2-phenyl, $-(CH_2)_n$-phenyl-(O-CH_2-phenyl)$_2$, $-CH_2$-phenyl-C(O)-benzothiazole or a moiety of the formulae:



wherein n is an integer from 0 to 3, Y is C_3-C_6 cycloalkyl, phenyl, benzyl, napthyl, pyridinyl, quinolyl, furyl, thienyl or pyrrolyl; rings of these groups being optionally substituted by from 1 to 3 substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NH_2$, $-NO_2$ or a five membered heterocyclic ring containing one heteroatom selected from N, S,; or

b) a moiety of the formulae $-(CH_2)_n$-A, $-(CH_2)_n$-S-A, or $-(CH_2)_n$-O-A, wherein A is the moiety:

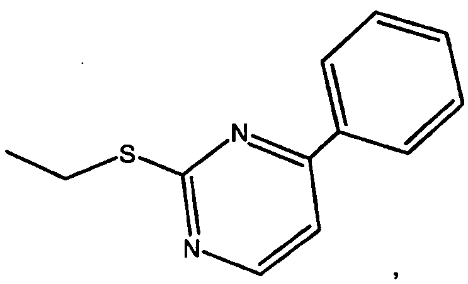


wherein

D is H, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, or $-CF_3$;

B and C are independently selected from phenyl, pyridinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, or $-NO_2$; or

c) a moiety of the formulae:



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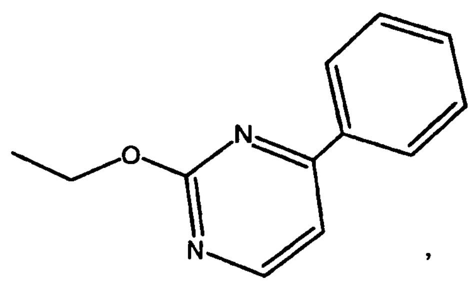

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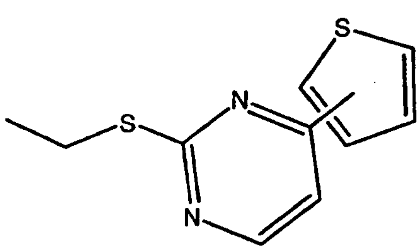

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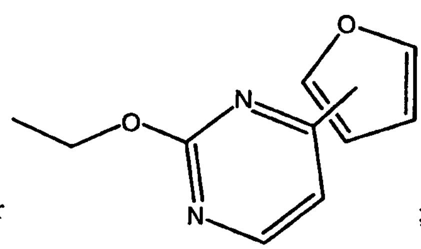
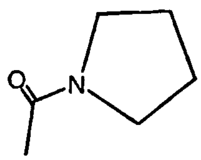


;

wherein the phenyl and pyrimidinyl rings of each moiety are optionally and independently substituted by from 1 to 3 substituents selected from halogen, $-CF_3$, -OH, $-C_1-C_6$ alkyl, C_1-C_6 alkoxy, or $-NO_2$;

R_4 is selected from H, halogen, $-CF_3$, -OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, benzyl, benzyloxy, phenyl, phenyloxy, -C(O)-phenyl, -C(O)-benzyl, $-CH_2-(C_3-C_6$ cycloalky), -C(O)-OH, -CH=O, $-C(O)-C_1-C_6$ alkyl, $-C(O)-O-C_1-C_6$ alkyl, $-C(O)-CF_3$, $-(CH_2)_n-S-CH_2-(C_3-C_6$ cycloalky),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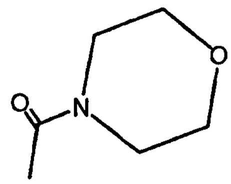
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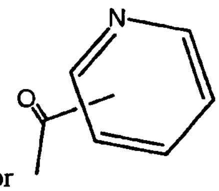
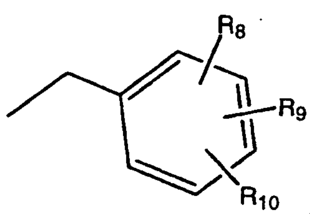

;

the phenyl and benzyl rings of the relevant R_3 groups being optionally substituted by from 1 to 3 groups selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, -C(O)-OH, or -OH;

n is an integer from 0 to 3;

R_5 is selected from -COOH, -C(O)-COOH, $-(CH_2)_n-C(O)-COOH$, $-(CH_2)_n-COOH$, -CH=CH-COOH,



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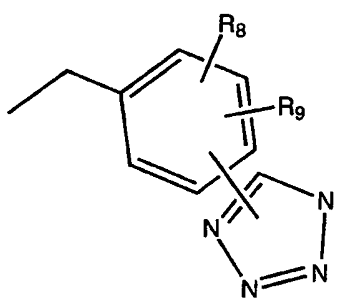

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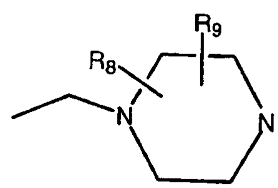

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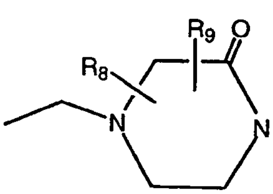

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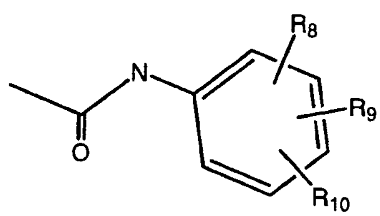

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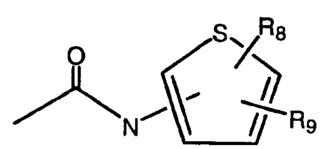

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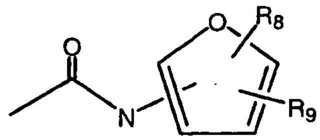

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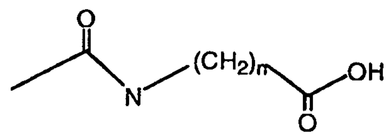

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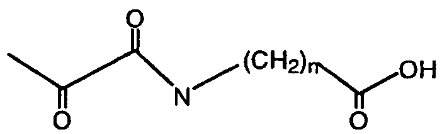

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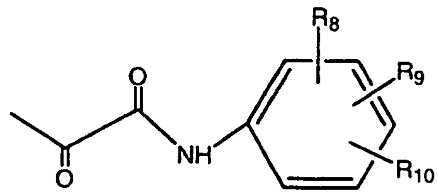

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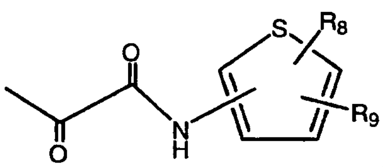

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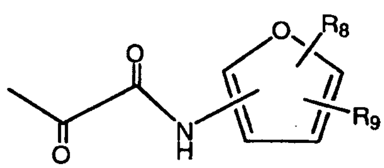

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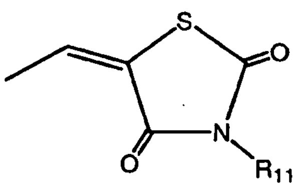

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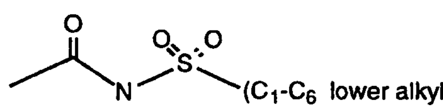

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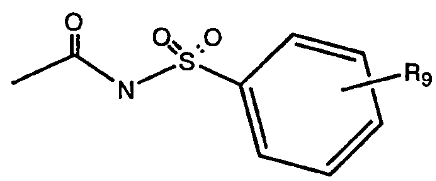
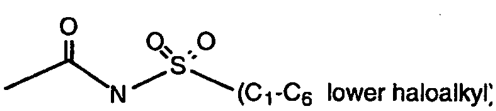
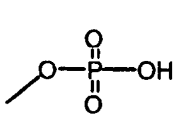




, ;

R_8 is selected from H, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, tetrazole,



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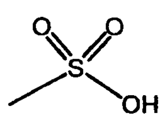
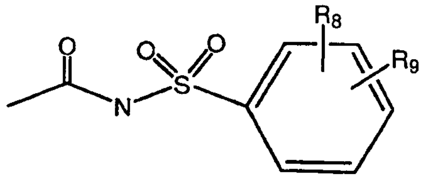


;

R_9 is selected from H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$;

R_{10} is selected from the group of H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH,

-$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$,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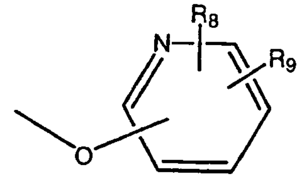
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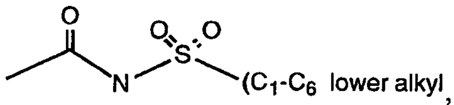
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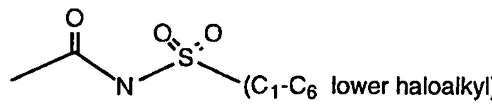
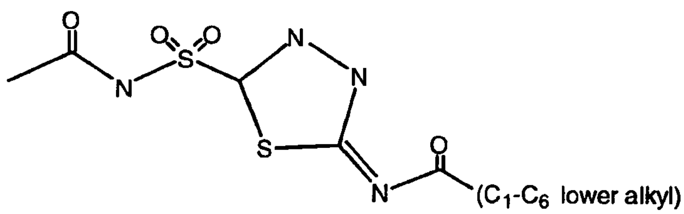
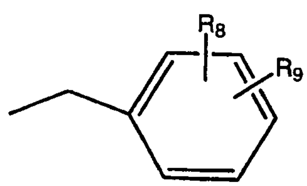
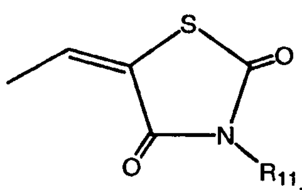

or


;

R_{11} is selected from H, C_1-C_6 lower alkyl, -CF_3, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, or


;

with a proviso that the complete moiety at the indole or indoline 1-position created by any combination of R_5, R_8, R_9, R_{10}, and/or R_{11} shall contain at least one acidic moiety selected from or containing a carboxylic acid, a tetrazole, or a moiety of the formulae: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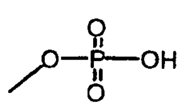
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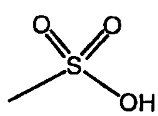
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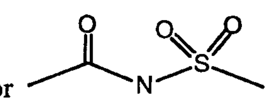
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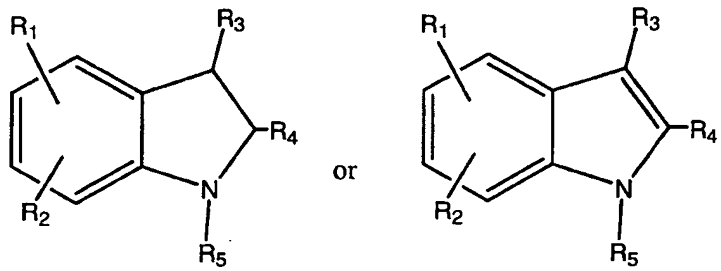
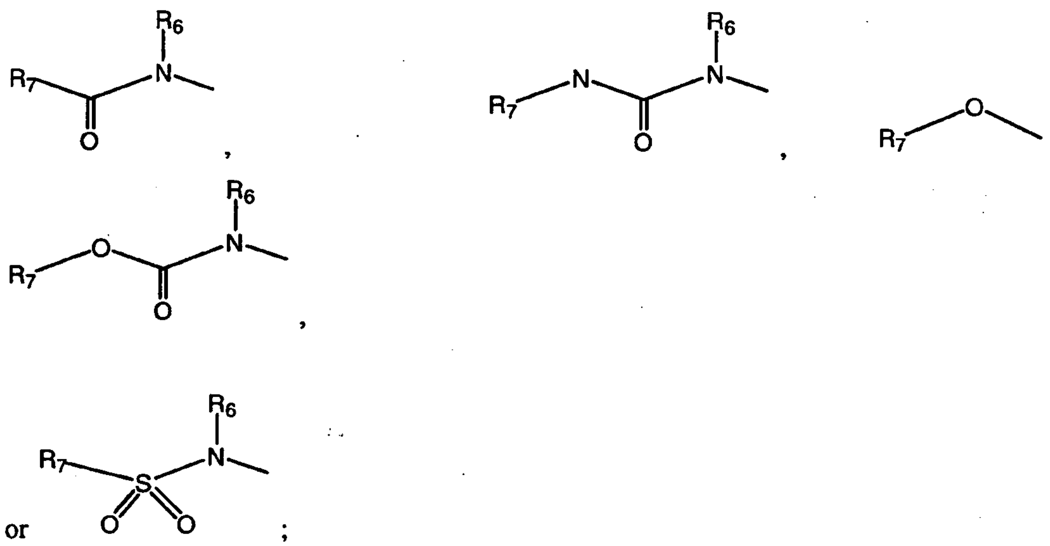
or a pharmaceutically acceptable salt thereof.

6. A compound of the formulae:



wherein:

R_1 is selected form H, halogen, $-CF_3$, -OH, $-C_1-C_6$ alkyl, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, phenyl, -O-phenyl, benzyl, -O-benzyl, -S-benzyl or a moiety of the formulae:



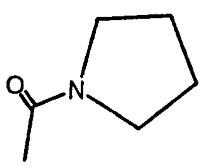
R_6 is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, -O-phenyl, benzyl, -O-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

R_7 is selected from $-(CH_2)_n$-COOH, $-(CH_2)_n-N-(C_1-C_6$ alkyl$)_2$, $-(CH_2)_n-NH-(C_1-C_6$ alkyl), $-CF_3$, C_1-C_6 alkyl, C_3-C_5 cycloalkyl, C_1-C_6 alkoxy, $-NH-(C_1-C_6$ alkyl), $-N-(C_1-C_6$ alkyl$)_2$, pyridinyl, thienyl, furyl, pyrrolyl, phenyl, -O-phenyl, benzyl, -O-benzyl, adamantyl, or morpholinyl, the pyridinyl, phenyl and benzyl rings of these groups being

optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

R_2 is selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_{10} alkyl, C_1-C_{10} alkoxy, -CHO, -CN, $-NO_2$, $-NH_2$, -NH-C_1-C_6 alkyl, -N(C_1-C_6 alkyl)$_2$, -N-SO_2-C_1-C_6 alkyl, or -SO_2-C_1-C_6 alkyl;

R_3 is selected from H, halogen, $-CF_3$, -OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, benzyl, benzyloxy, phenyl, phenyloxy, -C(O)-phenyl, -C(O)-benzyl, $-CH_2$-(C_3-C_5 cycloalky), -C(O)-OH, -CH=O, -C(O)-C_1-C_6 alkyl, -C(O)-O-C_1-C_6 alkyl, -C(O)-CF_3, -$(CH_2)_n$-S-CH_2-(C_3-C_5 cycloalky),



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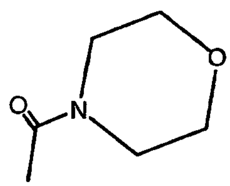

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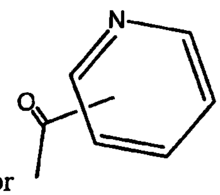


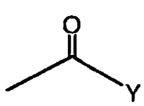
;

the phenyl and benzyl rings of the relevant R_3 groups being optionally substituted by from 1 to 3 groups selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, -C(O)-OH, or -OH;

n is an integer from 0 to 3;

R_4 is selected from the group of C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, -$(CH_2)_n$-C_3-C_5 cycloalkyl, -$(CH_2)_n$-S-$(CH_2)_n$-C_3-C_5 cycloalkyl, -$(CH_2)_n$-O-$(CH_2)_n$-C_3-C_5 cycloalkyl, or the groups of:

a) -$(CH_2)_n$-phenyl-O-phenyl, -$(CH_2)_n$-phenyl-CH_2-phenyl, -$(CH_2)_n$-O-phenyl-CH_2-phenyl, -$(CH_2)_n$-phenyl-(O-CH_2-phenyl)$_2$, -CH_2-phenyl-C(O)-benzothiazole or a moiety of the formulae:



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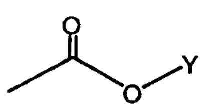

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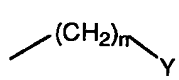

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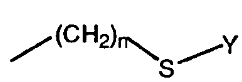

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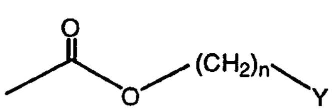

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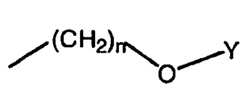

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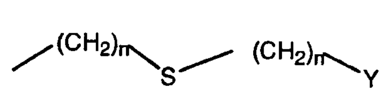
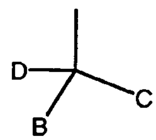


,

wherein n is an integer from 0 to 3, Y is C_3-C_6 cycloalkyl, phenyl, benzyl, napthyl, pyridinyl, quinolyl, furyl, thienyl or pyrrolyl; rings of these groups being optionally substituted by from 1 to 3 substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$ or a five membered heterocyclic ring containing one heteroatom selected from N, S,; or

b) a moiety of the formulae $-(CH_2)_n$-A, $-(CH_2)_n$-S-A, or $-(CH_2)_n$-O-A, wherein A is the moiety:

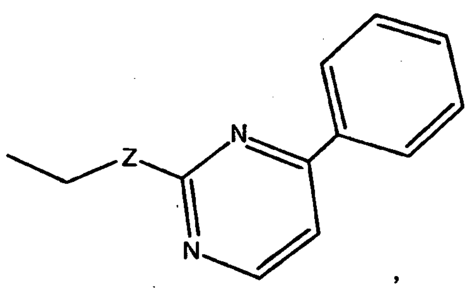


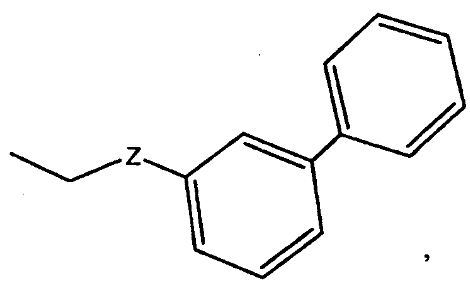
wherein

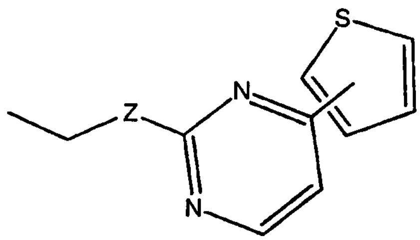
D is H, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, or $-CF_3$;

B and C are independently selected from phenyl, pyridinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, or $-NO_2$; or

c) a moiety of the formulae:



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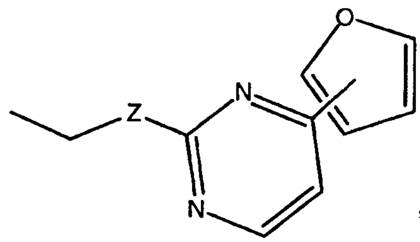
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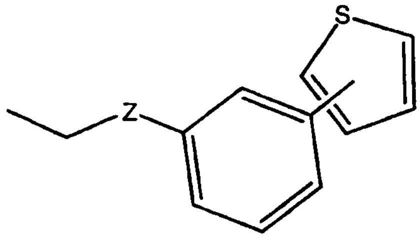
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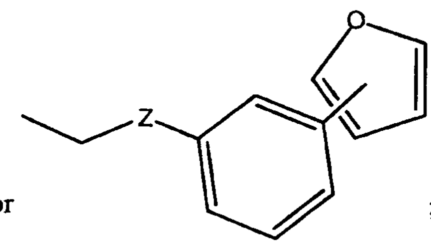
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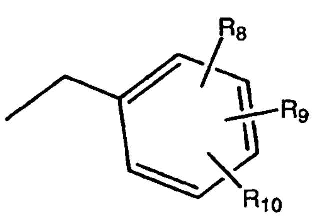
wherein Z is O or S and the phenyl and pyrimidinyl rings of each moiety are optionally and independently substituted by from 1 to 3 substituents selected from halogen, $-CF_3$, $-OH$, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, or $-NO_2$;

R_5 is selected from -COOH, -C(O)-COOH, $-(CH_2)_n$-C(O)-COOH, $-(CH_2)_n$-COOH, -CH=CH-COOH,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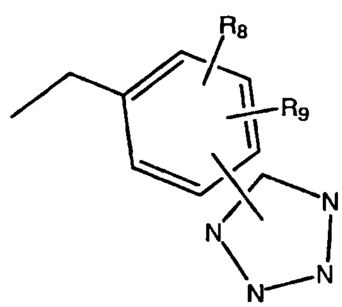
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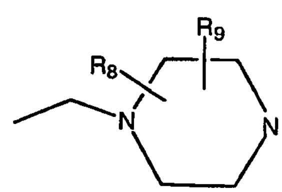
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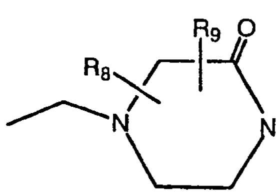
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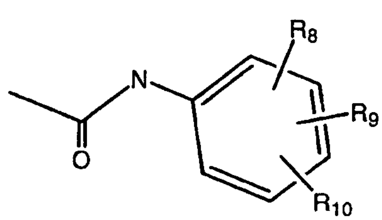
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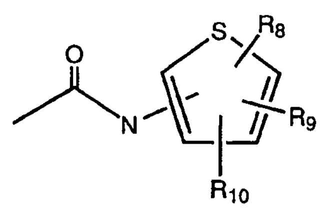
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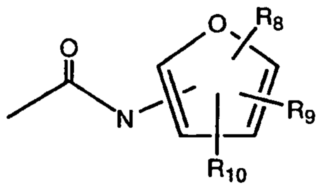
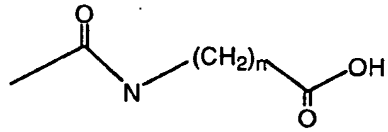
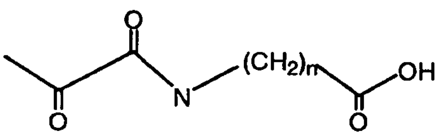
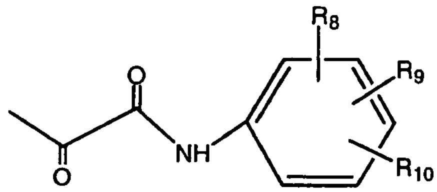
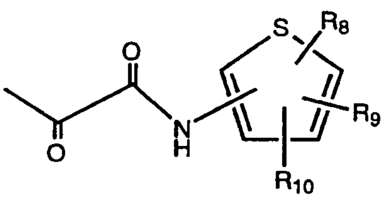
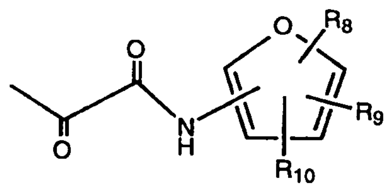
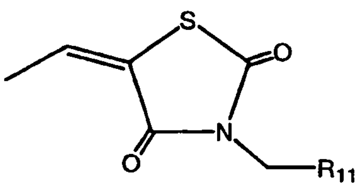
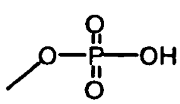
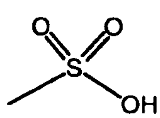
,
,

,
,

,
, or

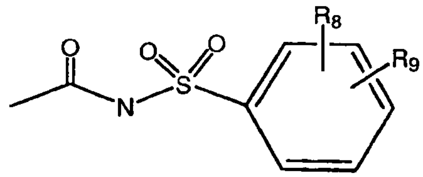
;

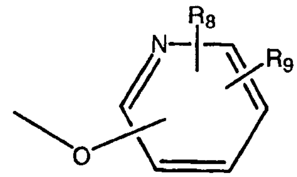
R_8 is selected from H, -COOH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH, tetrazole,

, or ;

R_9 is selected from H, halogen, $-CF_3$, -OH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH, $-C_1$-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$;

R_{10} is selected from the group of H, halogen, $-CF_3$, -OH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH, $-C_1$-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$,



, 

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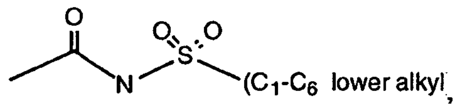
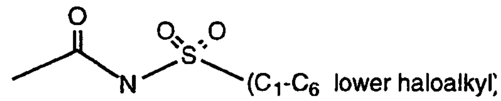


, 

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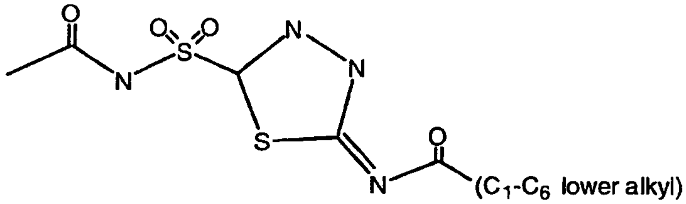
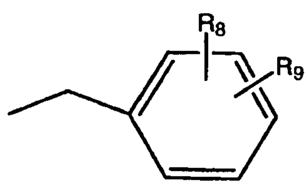


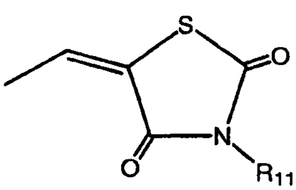
;

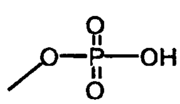
R_{11} is selected from H, C_1-C_6 lower alkyl, $-CF_3$, -COOH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH, or

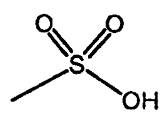


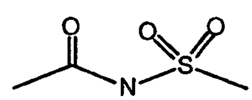
;

with a proviso that the complete moiety at the indole or indoline 1-position created by any combination of R_5, R_8, R_9, R_{10}, and/or R_{11} shall contain at least one acidic moiety selected from or containing a carboxylic acid, a tetrazole, or a moiety of the formulae:



, 

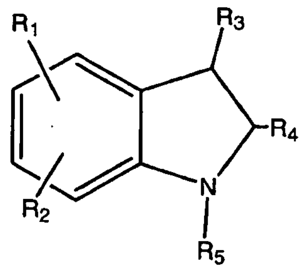
, 

or 

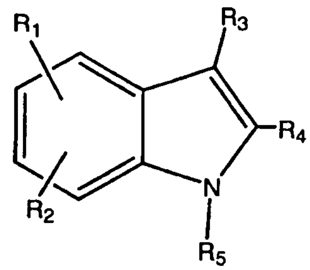
;

or a pharmaceutically acceptable salt thereof.

7. A compound of the formulae:

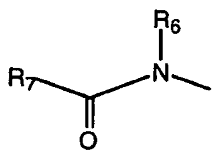


or



wherein:

R_1 is selected form H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-NH_2$, phenyl, -O-phenyl, benzyl, -O-benzyl, or a moiety of the formulae: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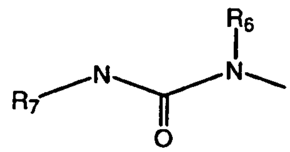
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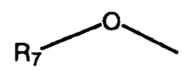
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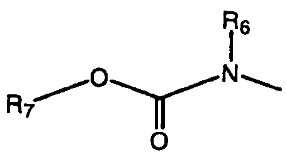
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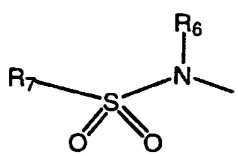
or  ;

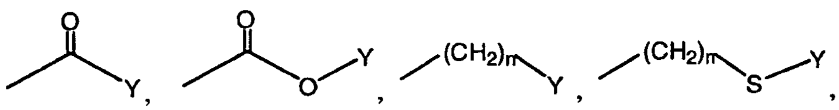
R_6 is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, -O-phenyl, benzyl, -O-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

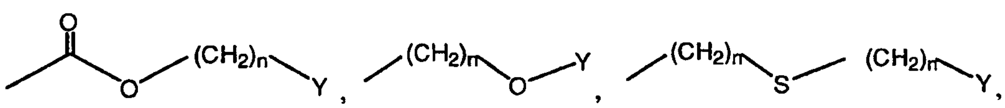
R_7 is selected from $-(CH_2)_n$-COOH, $-(CH_2)_n$-N-(C_1-C_6 alkyl$)_2$, $-(CH_2)_n$-NH-(C_1-C_6 alkyl), $-CF_3$, C_1-C_6 alkyl, C_3-C_5 cycloalkyl, C_1-C_6 alkoxy, -NH-(C_1-C_6 alkyl), -N-(C_1-C_6 alkyl$)_2$, pyridinyl, thienyl, furyl, pyrrolyl, phenyl, -O-phenyl, benzyl, -O-benzyl, adamantyl, or morpholinyl, the pyridinyl, phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

R_2 is selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_{10} alkyl, C_1-C_{10} alkoxy-CHO, -CN, -NO_2, $-NH_2$, -NH-C_1-C_6 alkyl, -N(C_1-C_6 alkyl)$_2$, -N-SO_2-C_1-C_6 alkyl, or -SO_2-C_1-C_6 alkyl;

R_3 is selected from the group of C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, -$(CH_2)_n$-C_3-C_6 cycloalkyl, -$(CH_2)_n$-S-$(CH_2)_n$-C_3-C_5 cycloalkyl, or the groups of:

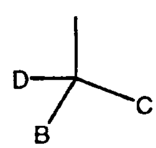
a) -$(CH_2)_n$-phenyl-O-phenyl, -$(CH_2)_n$-phenyl-CH_2-phenyl, -$(CH_2)_n$-O-phenyl-CH_2-phenyl, -$(CH_2)_n$-phenyl-(O-CH_2-phenyl)$_2$, -CH_2-phenyl-C(O)-benzothiazole or a moiety of the formulae:





wherein n is an integer from 0 to 3, Y is C_3-C_5 cycloalkyl, phenyl, benzyl, napthyl, pyridinyl, quinolyl, furyl, thienyl or pyrrolyl; rings of these groups being optionally substituted by from 1 to 3 substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$ or a five membered heterocyclic ring containing one heteroatom selected from N, S; or

b) a moiety of the formulae -$(CH_2)_n$-A, -$(CH_2)_n$-S-A, or -$(CH_2)_n$-O-A, wherein A is the moiety:

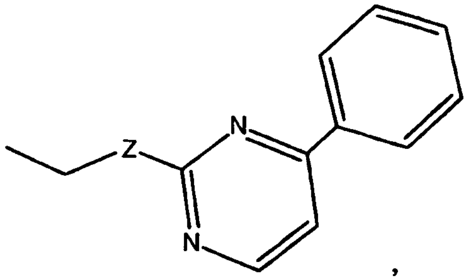
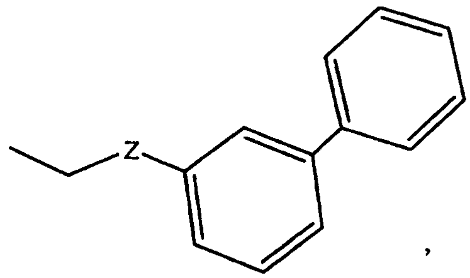


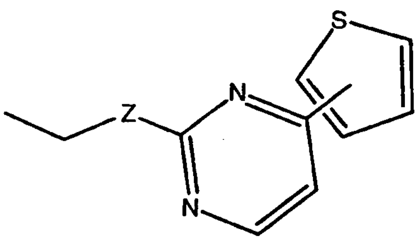
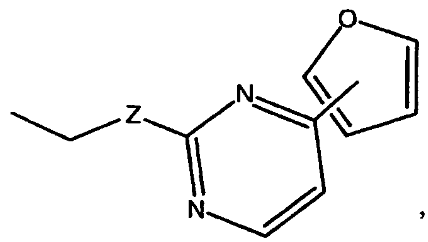
wherein

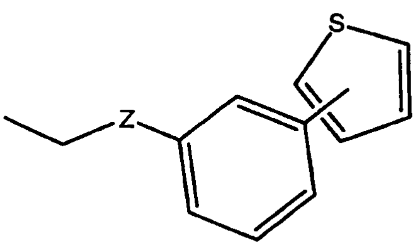
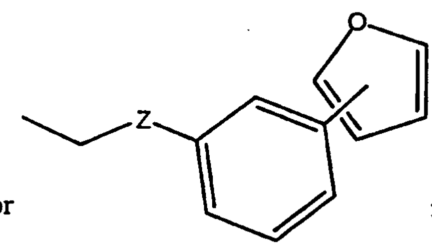
D is H, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, or $-CF_3$;

B and C are independently selected from phenyl, pyridinyl, furyl, thienyl or pyrrolyl groups, each optionally substituted by from 1 to 3, substituents selected from H, halogen, $-CF_3$, -OH, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, $-NH_2$ or $-NO_2$; or

c) a moiety of the formulae:

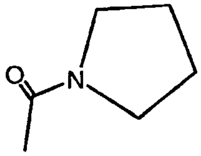
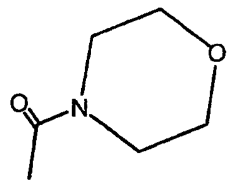
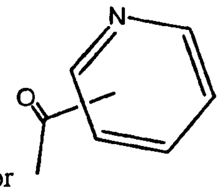
 ,
 ,

 ,
 ,

 , or
 ;

wherein Z is O or S and the phenyl and pyrimidinyl rings of each moiety are optionally and independently substituted by from 1 to 3 substituents selected from halogen, $-CF_3$, $-OH$, $-C_1$-C_6 alkyl, C_1-C_6 alkoxy, or $-NO_2$, $-NH_2$;

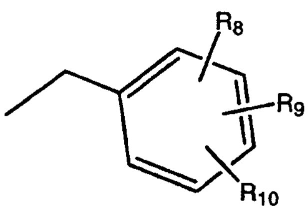
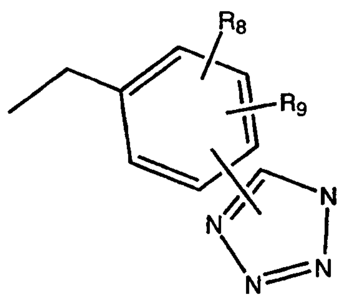
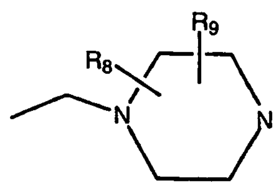
R_4 is selected from H, halogen, $-CF_3$, $-OH$, C_1-C_6 alkyl, C_1-C_6 alkoxy, benzyl, benzyloxy, phenyl, phenyloxy, -C(O)-phenyl, -C(O)-benzyl, $-CH_2$-(C_3-C_5 cycloalky), -C(O)-OH, -CH=O, -C(O)-C_1-C_6 alkyl, -C(O)-O-C_1-C_6 alkyl, -C(O)-CF_3, $-(CH_2)_n$-S-CH_2-(C_3-C_5 cycloalky),

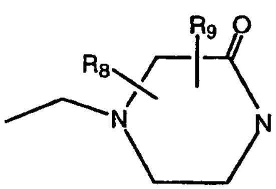
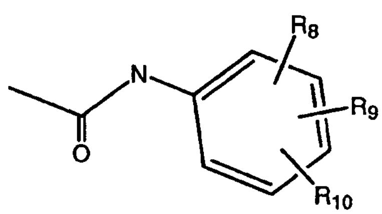
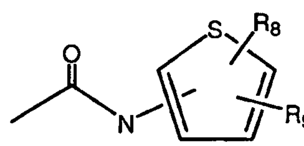
, , or ;

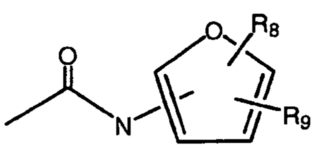
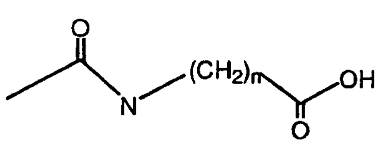
the phenyl and benzyl rings of the relevant R_3 groups being optionally substituted by from 1 to 3 groups selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, -C(O)-OH, or -OH;

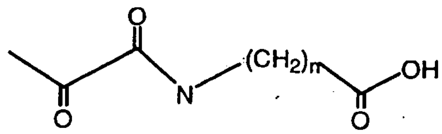
n is an integer from 0 to 3;

R_5 is selected from -COOH, -C(O)-COOH, $-(CH_2)_n$-C(O)-COOH, $-(CH_2)_n$-COOH, -CH=CH-COOH,

, , ,

, , ,

, ,



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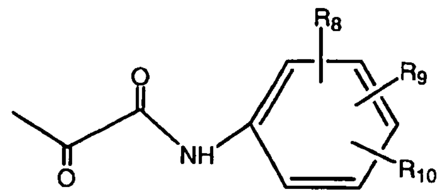

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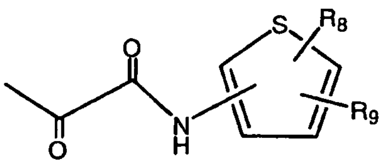

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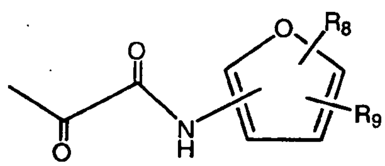

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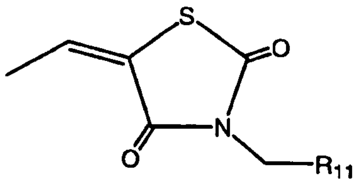
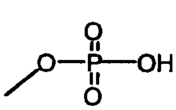


;

R_8 is selected from H, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, tetrazole,



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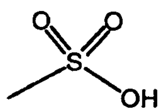
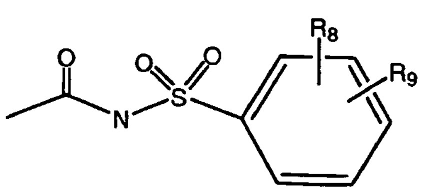


;

R_9 is selected from H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl$)_2$;

R_{10} is selected from the group of H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl$)_2$,



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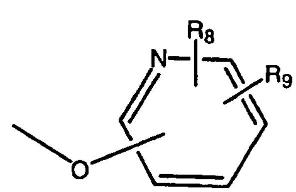

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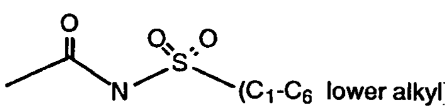

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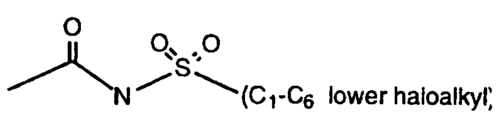
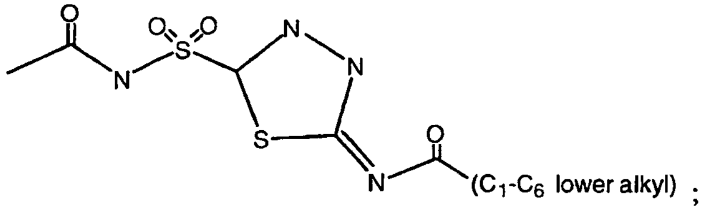
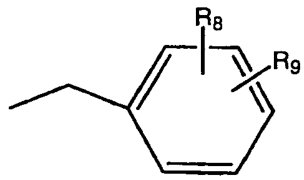


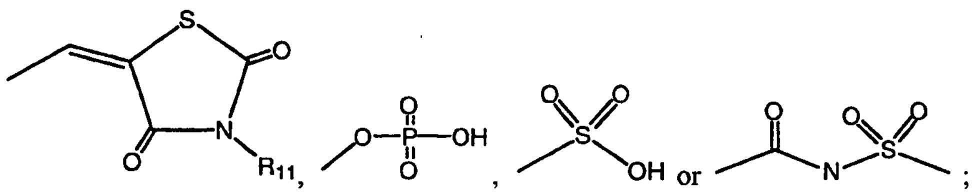
or



R_{11} is selected from H, C_1-C_6 lower alkyl, $-CF_3$, -COOH, $-(CH_2)_n$-COOH, $-(CH_2)_n$-C(O)-COOH, or

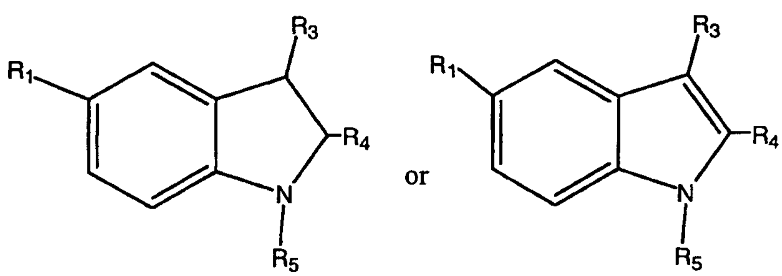


with a proviso that the complete moiety at the indole or indoline 1-position created by any combination of R_5, R_8, R_9, R_{10}, and/or R_{11} shall contain at least one acidic moiety selected from or containing a carboxylic acid, a tetrazole, or a moiety of the formulae:



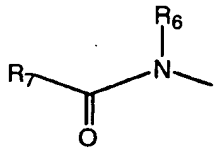
or a pharmaceutically acceptable salt thereof.

8. A compound of the formulae:



wherein:

R_1 is selected form $-NH_2$, -O-phenyl, benzyl, -O-benzyl, -N-benzyl, -N-benzyl-O-phenyl, -S-benzyl or a moiety of the formulae: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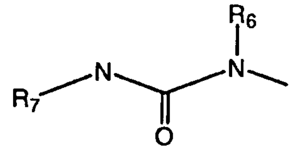
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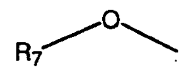
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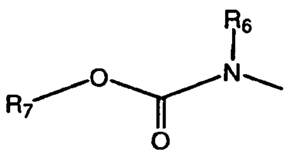
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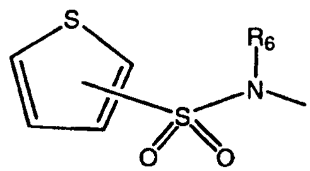
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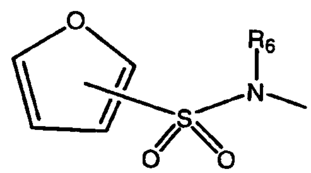
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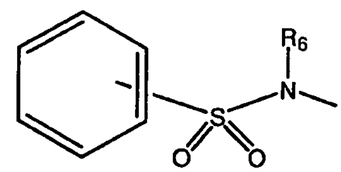
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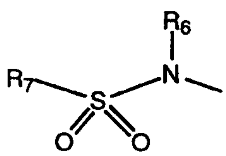

;

R_6 is selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, -O-phenyl, benzyl, -O-benzyl, the phenyl and benzyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

R_7 is selected from $-(CH_2)_n$-COOH, $-(CH_2)_n$-N-(C_1-C_6 alkyl$)_2$, $-(CH_2)_n$-NH-(C_1-C_6 alkyl), $-CF_3$, C_1-C_6 alkyl, C_3-C_5 cycloalkyl, C_1-C_6 alkoxy, -NH-(C_1-C_6 alkyl), -N-(C_1-C_6 alkyl$)_2$, pyridinyl, thienyl, furyl, pyrrolyl, phenyl, -O-phenyl, benzyl, -O-benzyl, adamantyl, or morpholinyl, the rings of these groups being optionally substituted by from 1 to 3 substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-CF_3$, or -OH;

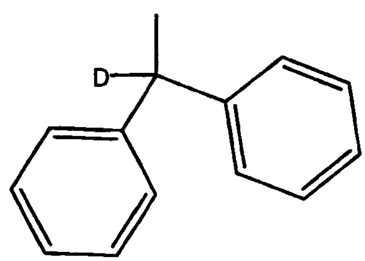
n is an integer from 0 to 3;

R_3 is selected from halogen, -C_1-C_6 alkyl, -C_1-C_6 alkoxy, -CF_3, -CH=O, -C(O)-C_1-C_6 alkyl, -C(O)-O-C_1-C_6 alkyl, -C(O)-OH, -C(O)-CF_3, -C(O)-phenyl, -C(O)-benzyl, -C(O)-pyrrolyl, -C(O)-thienyl, -C(O)-furanyl, or -C(O)-morpholinyl;

R_4 is selected from the group of -$(CH_2)_n$-C_3-C_6 cycloalkyl, -$(CH_2)_n$-S-$(CH_2)_n$-C_3-C_6 cycloalkyl, -$(CH_2)_n$-O-$(CH_2)_n$-C_3-C_6 cycloalkyl, -$(CH_2)_n$-S-C_1-C_6 alkyl, the groups of:

a) -C(O)-O-$(CH_2)_n$-C_3-C_5 cycloalkyl, -$(CH_2)_n$-phenyl, -$(CH_2)_n$-O-phenyl, -$(CH_2)_n$-S-phenyl, -$(CH_2)_n$-S-$(CH_2)_n$-phenyl, -$(CH_2)_n$-phenyl-O-phenyl, -$(CH_2)_n$-phenyl-CH_2-phenyl, -$(CH_2)_n$-O-phenyl-CH_2-phenyl, -$(CH_2)_n$-phenyl-(O-CH_2-phenyl$)_2$, -C(O)-O-phenyl, -C(O)-O-benzyl, -C(O)-O-pyridinyl, -C(O)-O-napthyl, -$(CH_2)_n$-S-napthyl, -$(CH_2)_n$-S-pyridinyl, -$(CH_2)_n$-pyridinyl or -$(CH_2)_n$-napthyl, -$(CH_2)_n$-O-napthyl, the phenyl, pyridinyl and napthyl rings of these groups being optionally substituted by from 1 to 3 substituents selected from H, halogen, -CF_3, -OH, -C_1-C_6 alkyl, C_1-C_6 alkoxy, -NO_2 or a five membered heterocyclic ring containing one heteroatom selected from N, S, or O; or

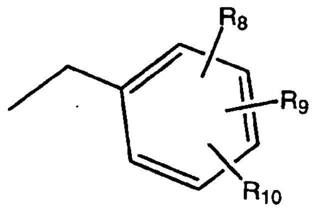
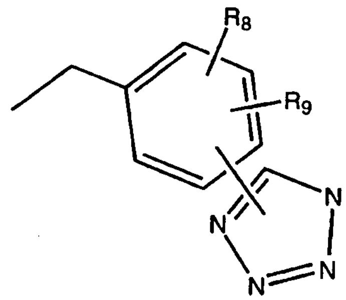
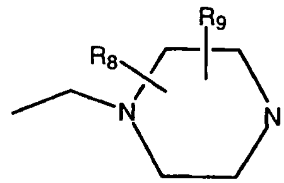
b) a moiety of the formulae -$(CH_2)_n$-A, -$(CH_2)_n$-S-A, or -$(CH_2)_n$-O-A, wherein A is the moiety:

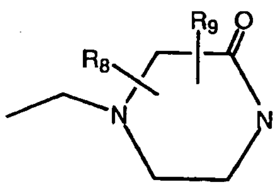
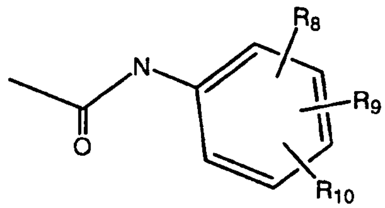
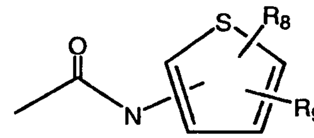


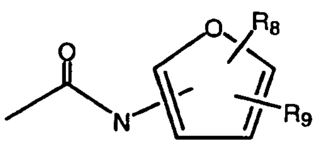
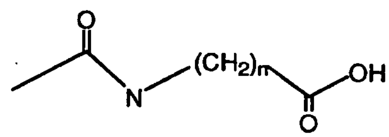
wherein

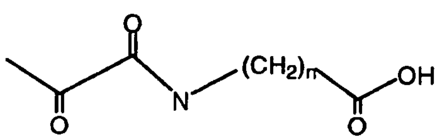
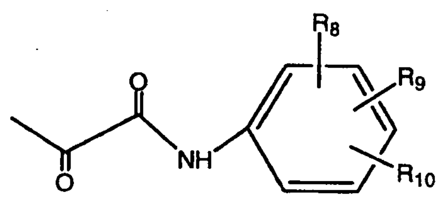
D is H, C_1-C_6 lower alkyl, C_1-C_6 lower alkoxy, or -CF_3;

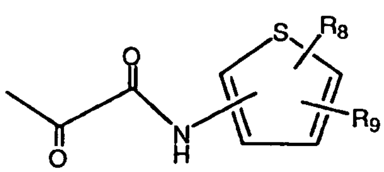
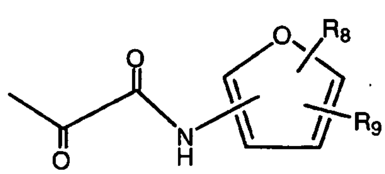
R_5 is selected from -COOH, -C(O)-COOH, -$(CH_2)_n$-C(O)-COOH, -$(CH_2)_n$-COOH, -CH=CH-COOH,

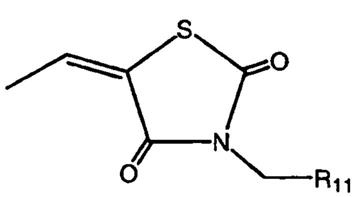
 ,  ,  ,

 ,  ,  ,

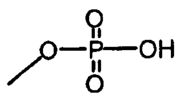
 ,  ,

 ,  ,

 ,  , or

 ;

R_8 is selected from H, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, tetrazole,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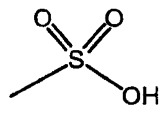
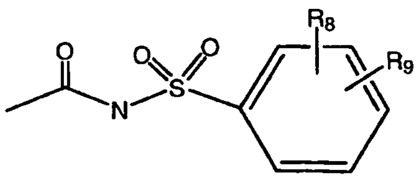

;

R_9 is selected from H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl$)_2$;

R_{10} is selected from the group of H, halogen, -CF_3, -OH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl$)_2$,



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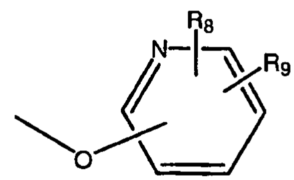

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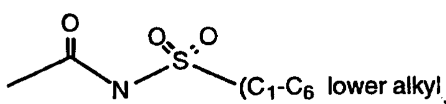

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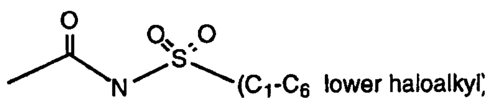

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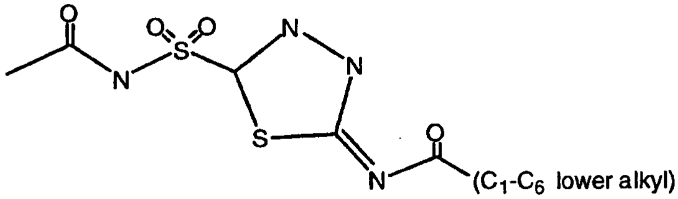
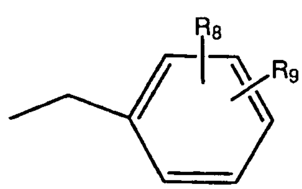


;

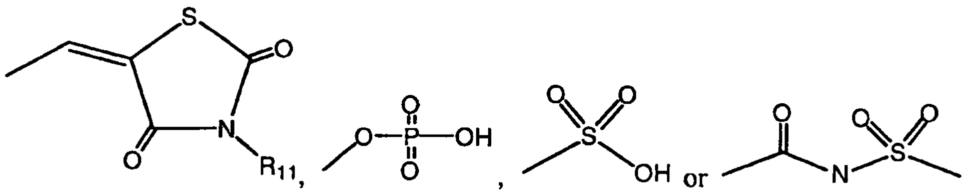
R_{11} is selected from H, C_1-C_6 lower alkyl, -CF_3, -COOH, -$(CH_2)_n$-COOH, -$(CH_2)_n$-C(O)-COOH, or



;

with a proviso that the complete moiety at the indole or indoline 1-position created by any combination of R_5, R_8, R_9, R_{10}, and/or R_{11} shall contain at least one acidic

moiety selected from or containing a carboxylic acid, a tetrazole, or a moiety of the formulae:



or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

10. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claim 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

11. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claim 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

12. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claim 7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

13. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claim 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

14. A compound of Claim 1 which is 4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(phenethylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

15. A compound of Claim 1 which is 4-[(3-chloro-5-[(cyclopentylcarbonyl)amino]-2-{[(2-furylmethyl)sulfanyl]methyl}-1H-indol-1-yl)methyl]benzoic acid or a pharmaceutically acceptable salt thereof.

16. A compound of Claim 1 which is 4-[(3-chloro-5-[(cyclopentylcarbonyl)amino]-2-{[(4-hydroxy-6-phenyl-2-pyrimidinyl)sulfanyl]methyl}-1H-indol-1-yl)methyl]benzoic acid or a pharmaceutically acceptable salt thereof.

17. A compound of Claim 1 which is 4-{[3-chloro-5-[(cyclopentylcarbonyl)amino]-2-({[4-(2-thienyl)-2-pyrimidinyl]sulfanyl}methyl)-1H-indol-1-yl]methyl}benzoic acid or a pharmaceutically acceptable salt thereof.

18. A compound of Claim 1 which is 4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(2,4-dibromophenoxy)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

19. A compound of Claim 1 which is 4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(cyclopentylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

20. A compound of Claim 1 which is 4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(propylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

21. A compound of Claim 1 which is 4-({2-{[4-(tert-butyl)phenoxy]methyl}-3-chloro-5-[(cyclopentylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

22. A compound of Claim 1 which is 4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(2-quinolinylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

23. A compound of Claim 1 which is 4-[(3-chloro-5-[(cyclopentylcarbonyl)amino]-2-{[(cyclopropylmethyl)sulfanyl]methyl}-1H-indol-1-yl)methyl]benzoic acid or a pharmaceutically acceptable salt thereof.

24. A compound of Claim 1 which is 4-({2-[(benzhydrylsulfanyl)methyl]-3-chloro-5-[(cyclopentylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

25. A compound of Claim 1 which is 4-({5-[(3-carboxypropanoyl)amino]-3-chloro-2-[(phenethylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

26. A compound of Claim 1 which is 4-[(5-[(3-carboxypropanoyl)amino]-3-chloro-2-{[(3-methylbenzyl)sulfanyl]methyl}-1H-indol-1-yl)methyl]benzoic acid or a pharmaceutically acceptable salt thereof.

27. A compound of Claim 1 which is 4-({2-({[4-(tert-butyl)benzyl]sulfanyl}methyl)-5-[(3-carboxypropanoyl)amino]-3-chloro-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

28. A compound of Claim 1 which is 4-({3-chloro-5-(3-furoylamino)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

29. A compound of Claim 1 which is 4-({5-(acetylamino)-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

30. A compound of Claim 1 which is 4-({3-chloro-5-{[3-(diethylamino)propanoyl]amino}-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

31. A compound of Claim 1 which is 4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(3-thienylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

32. A compound of Claim 1 which is 4-({5-{[(benzylamino)carbonyl]amino}-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

33. A compound of Claim 1 which is 4-({5-{[(butylamino)carbonyl]amino}-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

34. A compound of Claim 1 which is 3-[({1-(4-carboxybenzyl)-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-5-yl}amino)carbonyl]benzoic acid or a pharmaceutically acceptable salt thereof.

35. A compound of Claim 1 which is 4-{[5-(benzyloxy)-2-[(E)-2-carboxyethenyl]-3-(2-naphthoyl)-1H-indol-1-yl]methyl}benzoic acid or a pharmaceutically acceptable salt thereof.

36. A compound of Claim 1 which is 4-({3-acetyl-5-(benzyloxy)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

37. A compound of Claim 1 which is 4-{[5-(benzyloxy)-2-[(2-naphthylsulfanyl) methyl]-3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl]methyl}benzoic acid or a pharmaceutically acceptable salt thereof.

38. A compound of Claim 1 which is 4-({5-[(4-aminobutanoyl)amino]-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

39. A compound of Claim 1 which is 4-({3-chloro-5-[(cyclopentylcarbonyl)amino]-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

40. A compound of Claim 1 which is 4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(2-quinoxalinylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

41. A compound of Claim 1 which is 4-({3-chloro-5-[(2,2-dimethylpropanoyl)amino]-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

42. A compound of Claim 1 which is 4-({5-{[(benzyloxy)carbonyl]amino}-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

43. A compound of Claim 1 which is 4-({3-chloro-5-{[(cyclopentyloxy)carbonyl] amino}-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

44. A compound of Claim 1 which is 4-({5-(acetylamino)-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

45. A compound of Claim 1 which is 4-({5-{[(butylamino)carbonyl]amino}-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

46. A compound of Claim 1 which is 4-({5-{[(butylamino)carbonyl]amino}-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

47. A compound of Claim 1 which is 4-({3-chloro-5-[(morpholinocarbonyl)amino]-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

48. A compound of Claim 1 which is 4-({5-(benzylamino)-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

49. A compound of Claim 1 which is 4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(3-phenoxybenzyl)amino]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

50. A compound of Claim 1 which is 4-({3-chloro-5-[(cyclopentylcarbonyl)(methyl)amino]-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

51. A compound of Claim 1 which is 4-({5-[acetyl(benzyl)amino]-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

52. A compound of Claim 1 which is 4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(tetrahydro-3-furanylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

53. A compound of Claim 1 which is 4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(3-thienylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

54. A compound of Claim 1 which is 4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(1-adamantylcarbonyl)amino]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

55. A compound of Claim 1 which is 3-[({1-(4-carboxybenzyl)-3-chloro-2-[(2-naphthylsulfanyl)methyl]-1H-indol-5-yl}amino)carbonyl]benzoic acid or a pharmaceutically acceptable salt thereof.

56. A compound of Claim 1 which is 4-({3-chloro-2-[(2-naphthylsulfanyl)methyl]-5-[(3-phenylpropanoyl)amino]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

57. A compound of Claim 1 which is 4-({5-amino-3-chloro-2-[(2-naphthylsulfanyl) methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

58. A compound of Claim 1 which is N-{3-chloro-1-(4-{[(methylsulfonyl)amino] carbonyl}benzyl)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-5-yl}cyclopentanecarboxamide or a pharmaceutically acceptable salt thereof.

59. A compound of Claim 1 which is N-{3-chloro-2-[(2-naphthylsulfanyl)methyl]-1-[4-({[(4-nitrophenyl)sulfonyl] amino}carbonyl)benzyl]-1H-indol-5-yl}cyclopentanecarboxamide or a pharmaceutically acceptable salt thereof.

60. A compound of Claim 1 which is N-{3-chloro-1-[4-({[(2-methylphenyl) sulfonyl]amino}carbonyl)benzyl]-2-[(2-naphthylsulfanyl)methyl]-1H-indol-5-yl}cyclopentanecarboxamide or a pharmaceutically acceptable salt thereof.

61. A compound of Claim 1 which is N-[3-chloro-2-[(2-naphthylsulfanyl)methyl]-1-(4-{[(phenylsulfonyl)amino] carbonyl}benzyl)-1H-indol-5-yl]cyclopentanecarboxamide or a pharmaceutically acceptable salt thereof.

62. A compound of Claim 1 which is N-{3-chloro-2-[(2-naphthylsulfanyl)methyl]-1-[4-({[(trifluoromethyl)sulfonyl] amino}carbonyl)benzyl]-1H-indol-5-yl}cyclopentanecarboxamide or a pharmaceutically acceptable salt thereof.

63. A compound of Claim 1 which is 4-[5-[(cyclopentylcarbonyl)amino]-2-[(2-naphthyloxy)methyl]-3-(1-pyrrolidinylcarbonyl)-1H-indol-1-yl]butanoic acid or a pharmaceutically acceptable salt thereof.

64. A compound of Claim 1 which is 4-{5-[(cyclopentylcarbonyl)amino]-3-(morpholinocarbonyl)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoic acid or a pharmaceutically acceptable salt thereof.

65. A compound of Claim 1 which is N-[2-[(2-naphthyloxy)methyl]-1-(4-oxo-4-{[(trifluoromethyl)sulfonyl]amino}butyl)-3-(1-pyrrolidinylcarbonyl)-1H-indol-5-yl]cyclopentanecarboxamide or a pharmaceutically acceptable salt thereof.

66. A compound of Claim 1 which is N-[3-(morpholinocarbonyl)-2-[(2-naphthyloxy)methyl]-1-(4-oxo-4-{[(trifluoro-methyl)sulfonyl]amino}butyl)-1H-indol-5-yl]cyclopentanecarboxamide or a pharmaceutically acceptable salt thereof.

67. A compound of Claim 1 which is 5-[(cyclopentylcarbonyl)amino]-2-[(2-naphthyloxy)methyl]-1-(4-oxo-4-{[(trifluoromethyl)sulfonyl]amino}butyl)-1H-indole-3-carboxylic acid or a pharmaceutically acceptable salt thereof.

68. A compound of Claim 1 which is 2-(4-{[5-(benzyloxy)-3-(1-naphthoyl)-1H-indol-1-yl]methyl}phenyl)acetic acid or a pharmaceutically acceptable salt thereof.

69. A compound of Claim 1 which is 2-(4-{[5-(benzyloxy)-3-(2-naphthoyl)-1H-indol-1-yl]methyl}phenyl)acetic acid or a pharmaceutically acceptable salt thereof.

70. A compound of Claim 1 which is 2-[4-({5-(benzyloxy)-3-[3,5-bis(trifluoromethyl)benzoyl]-1H-indol-1-yl}methyl)phenyl]acetic acid or a pharmaceutically acceptable salt thereof.

71. A compound of Claim 1 which is 4-({3-benzoyl-5-(benzyloxy)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

72. A compound of Claim 1 which is 4-({5-(benzyloxy)-3-isobutyryl-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

73. A compound of Claim 1 which is 2-{3-acetyl-5-(benzyloxy)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}acetic acid or a pharmaceutically acceptable salt thereof.

74. A compound of Claim 1 which is 2-{5-(benzyloxy)-3-isobutyryl-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}acetic acid or a pharmaceutically acceptable salt thereof.

75. A compound of Claim 1 which is 4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoic acid or a pharmaceutically acceptable salt thereof.

76. A compound of Claim 1 which is 3-[(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]benzoic acid or a pharmaceutically acceptable salt thereof.

77. A compound of Claim 1 which is 4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-N-[3({[(trifluoromethyl)sulfonyl]amino}carbonyl)phenyl]butanamide or a pharmaceutically acceptable salt thereof.

78. A compound of Claim 1 which is 4-[(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]benzoic acid or a pharmaceutically acceptable salt thereof.

79. A compound of Claim 1 which is 2-[(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]benzoic acid or a pharmaceutically acceptable salt thereof.

80. A compound of Claim 1 which is 3-[(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]propanoic acid or a pharmaceutically acceptable salt thereof.

81. A compound of Claim 1 which is 3-[(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]propanoic acid or a pharmaceutically acceptable salt thereof.

82. A compound of Claim 1 which is N-(4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)-2-methylbenzenesulfonamide or a pharmaceutically acceptable salt thereof.

83. A compound of Claim 1 which is 5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}pentanoic acid or a pharmaceutically acceptable salt thereof.

84. A compound of Claim 1 which is 3-[(5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}pentanoyl)amino]benzoic acid or a pharmaceutically acceptable salt thereof.

85. A compound of Claim 1 which is 5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-N-[3-({[(trifluoromethyl)sulfonyl]amino}carbonyl)phenyl]pentanamide or a pharmaceutically acceptable salt thereof.

86. A compound of Claim 1 which is 2-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}acetic acid or a pharmaceutically acceptable salt thereof.

87. A compound of Claim 1 which is (E)-4-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-2-butenoic acid or a pharmaceutically acceptable salt thereof.

88. A compound of Claim 1 which is 3-({3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}methyl)benzoic acid or a pharmaceutically acceptable salt thereof.

89. A compound of Claim 1 which is 1-{1-[4-(1,3-benzothiazol-2-ylcarbonyl)benzyl]-5-(benzylsulfanyl)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-3-yl}-1-ethanone or a pharmaceutically acceptable salt thereof.

90. A compound of Claim 1 which is 1-{1-[3-(1,3-benzothiazol-2-ylcarbonyl)benzyl]-5-(benzylsulfanyl)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-3-yl}-1-ethanone or a pharmaceutically acceptable salt thereof.

91. A compound of Claim 1 which is 2-[3-({3-acetyl-5-(benzyloxy)-2-[(2-naphthylsulfanyl)methyl]-1H-indol-1-yl}methyl)benzoyl]-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof.

92. A compound of Claim 1 which is 5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-2-oxopentanoic acid or a pharmaceutically acceptable salt thereof.

93. A compound of Claim 1 which is 3-[(5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-2-oxopentanoyl)amino]benzoic acid or a pharmaceutically acceptable salt thereof.

94. A compound of Claim 1 which is 4-[(5-{3-benzoyl-5-(benzyloxy)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}-2-oxopentanoyl)amino]benzoic acid or a pharmaceutically acceptable salt thereof.

95. A compound of Claim 1 which is 3-({4-[5-[(cyclopentylcarbonyl)amino]-2-[(2-naphthyloxy)methyl]-3-(1-pyrrolidinylcarbonyl)-1H-indol-1-yl]butanoyl}amino)benzoic acid or a pharmaceutically acceptable salt thereof.

96. A compound of Claim 1 which is 3-[(4-{5-[(cyclopentylcarbonyl)amino]-3-(morpholinocarbonyl)-2-[(2-naphthyloxy)methyl]-1H-indol-1-yl}butanoyl)amino]benzoic acid
or a pharmaceutically acceptable salt thereof.

97. A compound of Claim 1 which is N-[2-[(2-naphthyloxy)methyl]-1-{4-oxo-4-[3-({[(trifluoromethyl)sulfonyl]amino}carbonyl)anilino]butyl}-3-(1-pyrrolidinylcarbonyl)-1H-indol-5-yl]cyclopentanecarboxamide or a pharmaceutically acceptable salt thereof.

98. A compound of Claim 1 which is N-(3-(morpholinocarbonyl)-2-[(2-naphthyloxy)methyl]-1-{4-oxo-4-[3-({[(trifluoromethyl)sulfonyl]amino}carbonyl)anilino]butyl}-1H-indol-5-yl)cyclopentanecarboxamide or a pharmaceutically acceptable salt thereof.

99. A compound of Claim 1 which is 2-(4-{[5-(benzyloxy)-3-(1-naphthoyl)-1H-indol-1-yl]methyl}phenyl)acetic acid or a pharmaceutically acceptable salt thereof.

100. A method of inhibiting the phospholipase activity of an enzyme in a mammalian subject in need thereof comprising adminstering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 9.

101. A method of inhibiting the phospholipase activity of an enzyme in a mammalian subject in need thereof comprising adminstering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 10.

102. A method of inhibiting the phospholipase activity of an enzyme in a mammalian subject in need thereof comprising adminstering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 11.

103. A method of inhibiting the phospholipase activity of an enzyme in a mammalian subject in need thereof comprising adminstering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 12.

104. A method of inhibiting the phospholipase activity of an enzyme in a mammalian subject in need thereof comprising adminstering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 13.

105. A method of treating an inflammatory response in a mammalian subject in need thereof comprising adminstering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 9.

106. A method of treating an inflammatory response in a mammalian subject in need thereof comprising adminstering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 10.

107. A method of treating an inflammatory response in a mammalian subject in need thereof comprising adminstering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 11.

108. A method of treating an inflammatory response in a mammalian subject in need thereof comprising adminstering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 12.

109. A method of treating an inflammatory response in a mammalian subject in need thereof comprising adminstering to said subject a therapeutically effective amount of a pharmaceutical composition of claim 13.